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Enhancing effect of taurine on CYP7A1 mRNA expression in Hep G2 cells

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Summary. Taurine has been reported to enhance cholesterol 7α-hydroxylase (CYP7A1) mRNA expression in animal models. However, no *in vitro* studies of this effect have been reported. The Hep G2 human hepatoma cell line has been recognized as a good model for studying the regulation of human CYP7A1. This work characterizes the effects of taurine on CYP7A1 mRNA levels of Hep G2 cells in a dose- and time-dependent manner. In the dose-dependent experiment, Hep G2 cells were treated with 0, 2, 10 or 20 mM taurine in the presence or absence of cholesterol 0.2 mM for 48 h. In the time-dependent experiment, Hep G2 cells were treated with 0 or 20 mM taurine for 4, 24 and 48 h with and without cholesterol 0.2 mM. Our data revealed that taurine showed time- and dose-response effects on CYP7A1 mRNA levels in Hep G2 cells. However, glycine – a structural analogue of taurine – did not have an effect on CYP7A1 gene expression. These results show that, in agreement to previous studies on animal models, taurine induces the mRNA levels of CYP7A1 in Hep G2 cells, which could enhance cholesterol conversion into bile acids. Also, Hep G2 cell line may be an appropriate model to study the effects of taurine on human cholesterol metabolism.

Keywords: Taurine – CYP7A1 – Hep G2 – Cholesterol

Introduction

Cholesterol conversion to bile acids plays a vital role in the elimination of cholesterol, which is one of the main factors regulating cholesterol homeostasis in the body (Sjovall, 2004). This process occurs via the "classic" (neutral) or the "alternative" (acidic) bile acid biosynthesis pathways (Javitt, 1994). The first and rate-limiting reaction of the classic pathway is the 7α-hydroxylation of cholesterol, which is catalyzed by cholesterol 7α-hydroxylase, a product of a liver-specific microsomal cytochrome P450 gene (CYP7A1) (Myant and Mitropoulos, 1977; Jelinek et al., 1990; Nelson et al., 1996). There is evidence suggesting that the transcriptional level of cholesterol 7α-hydroxylase is regulated by a wide range of diverse stimuli, including bile acids, steroid hormones, thyroid hormones, cytokines, insulin, retinoids, and cholesterol (Li et al., 1990; Russell and Setchell, 1992; Chiang, 1998).

Taurine, 2-aminoethanesulfonic acid, which is present freely at high concentrations in mammalian plasma and cells, has been reported to play an important role in several essential biological and physiological functions, such as brain and retinal development, calcium modulation, membrane stabilization, reproduction, immunity, antioxidation, detoxification and osmoregulation (Huxtable, 1992; Sturman, 1993; Wight et al., 1986; Kuriyama, 1980; Thurston et al., 1980; Pasantes-Morales et al., 1985). In recent years, the role of taurine in cholesterol metabolism has received considerable attention. We have reported on the effect of taurine on cholesterol profile in rats and mice (Yokogoshi et al., 1999; Nishimura et al., 2003; Mochizuki et al., 1998; Chen et al., 2004). Taurine has also been demonstrated to reduce cholesterol in other species, such as hamsters, guinea pigs, rabbits and human (Murakami et al., 2002; Cantafora, 1986; Herrmann, 1959; Zhang et al., 2004). We also reported that the hypocholesterolemic effects of taurine were mainly due to the enhancement of cholesterol degeneration and the excretion of bile acids via its ability to enhance CYP7A1 mRNA activity and mRNA level in rats (Yokogoshi

et al., 1999). Until now there have been few studies on the effects of taurine on CYP7A1 gene expression *in vitro*.

Hep G2 cells, a well-characterized human hepatoblastoma cell line, have been used to study cholesterol homeostatic functions, including apolipoproteins, low-density lipoprotein receptor, enzymes involved in synthesis and degeneration of cholesterol (Axelson et al., 1991; Craig et al., 1988; Ellsworth et al., 1991). Recent reports have supported the application of Hep G2 as a good model to study the molecular basis of human CYP7A1 regulation (Pandak et al., 1996; Taniguchi, 1994).

In the present report, we elucidated the dose- and time-dependent response of Hep G2 cells to taurine treatment. We further examined the effect of glycine, a structural analogue of taurine, on CYP7A1 gene expression, comparing its response to that of taurine.

Materials and methods

Cell culture

The human hepatocellular carcinoma (Hep G2) cell line was obtained from Riken Cell Bank (Japan) and was maintained as monolayer culture in Dulbecco's Modified Eagle Medium (DMEM, Sigma, USA) supplemented with 10% fetal calf serum (Sigma), 1% antibiotic antimycotic solution (Sigma), 0.02 M N-2-hydroxyethylpiperazine-N-2-ethanesulphonic acid (HEPES, Sigma), 0.01 g/l transferrin (Gibco, USA), 1% non-essential amino acids (Gibco). The cells were kept in an atmospheric mixture of 5% CO_2 and 95% air at 37°C. The culture medium was changed every 3 days. The cells were subcultivated by using 0.05% Trypsin/0.53 mM EDTA (Gibco).

Cell treatments

Hep G2 cells were seeded into 35 mm dishes and grown until confluent. At confluence, the medium was replaced by serum-free medium, and the cells were cultured for 24 h prior to treatment. Samples used to treat the cells included taurine (Sigma), cholesterol in form of water-soluble cholesterol (Sigma) and glycine (Sigma). Sample concentrations and treatment time are indicated in the result section and figure legends. Sample solutions were made by using serum-free medium. Cell viability was checked during experiments by using trypan blue dye exclusion test, with cell survival rate more than 95%.

RNA isolation and first-strand cDNA synthesis

Total RNA was isolated from Hep G2 cells using TRIzol reagent (Invitrogen, USA) according to the manufacturer's instructions and stored at −80°C. Five micrograms of total RNA was reverse transcribed using oligo(dT) with the SuperScript First-Strand Synthesis System for RT-PCR (Invitrogen). cDNA synthesis was performed in a final volume of 20 μl, and the resulting cDNA was stored at −20°C until PCR.

Semi-quantification of mRNA levels by reverse transcription PCR

In the preliminary experiment, we used reverse transcription PCR (RT-PCR) for semi-quantitation of mRNA levels. First-strand cDNA was subjected to PCR with Takara ExTaq (Takara, Japan) and carried out in a total volume of 12 μl reaction mixture using the Takara Thermal Cycler (Takara). The amplified products were analyzed by electrophoresis on 10 g/l agarose gel in TBE buffer. The gels were then stained with SYBR Green I nucleic acid gel stain (BioWhitaker Molecular Applications, USA) for 30 minutes. The PCR product was visualized under UV light and analyzed for the density of amplified cDNA using FlourImager SI with Image Quant software (Molecular Dynamics, USA).

Quantification of mRNA levels by real-time PCR

A real-time hot-start PCR was performed with the LightCycler FastStart DNA Master SYBR Green I Kit (Roche Diagnostics, Germany). The amplification was carried out in a total volume of 20 μl reaction mixture on a LightCycler Instrument (Roche Diagnostics). Data analyses were performed using LightCycler software version 3.5 (Roche Diagnostics).

Real-time PCR was used for quantitation of mRNA levels in the time- and dose-response experiments and comparison between taurine and glycine.

Oligonucleotide primers for human CYP7A1 and GAPDH genes were designed using the software Primer3 (Rozen and Skaletsky, 2000) from the GenBank cDNA sequences of human CYP7A1 (accession no. NM000780) and GAPDH (accession no. NM002046) and synthesized by Kurabo (Japan). The differential gene expressions were normalized using corresponding GAPDH expression level.

Statistical analysis

Statistical evaluation of data was performed by Student's t-test or one-way analysis of variance followed by Turkey's multiple comparison test, when which is appropriate, using the software Minitab version 13.32. A p value of less than 0.05 was considered to be statistically significant.

Results

Preliminary experiment: Effects of taurine on CYP7A1 gene expression

In the preliminary experiment, we cultured Hep G2 cells in 20 mM taurine and/or 0.2 mM cholesterol for 48 h. RNA from the cells was extracted and RT-PCR was performed for semi-quantitation of CYP7A1 mRNA level. The groups with either taurine or cholesterol + taurine treatments showed a significant induction of CYP7A1 mRNA levels compared to their respective controls, taurine(−)-cholesterol(−) group or taurine(+)-cholesterol(−) group (Fig. 1). This result inspired us to perform a more detailed study, examining the effects of taurine on CYP7A1 gene expression in a dose and time response.

Effects of dose-dependent treatment of taurine on CYP7A1 gene expression

The expression profile of CYP7A1 was determined in Hep G2 cells treated with various concentrations of taurine. To accomplish this, taurine of concentrations of 0, 2, 10 or 20 mM was applied to the Hep G2 cells for 48 h. Taurine at 2 mM induced the expression of CYP7A1 gene expression, with a greater effect achieved at concentrations of 10 and 20 mM (Fig. 2).

In another experiment, Hep G2 cells were cultured with 0.2 mM cholesterol and varying concentrations of taurine:

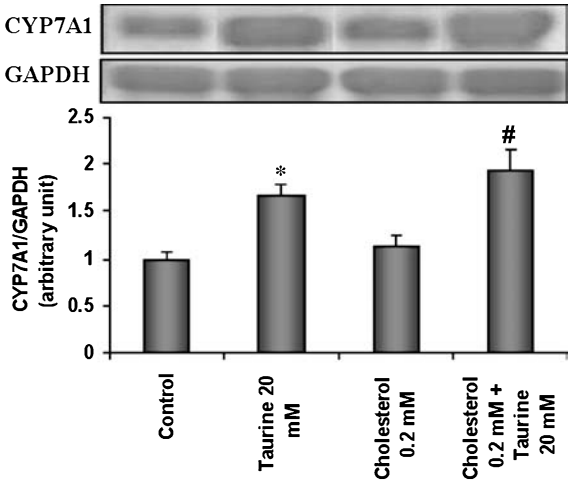

Fig. 1. Effect of taurine on CYP7A1 mRNA expression in Hep G2 cells. Hep G2 cells were cultured to confluence, changed into serum-free medium for 24 h, treated with taurine 20 mM and/or cholesterol 0.2 mM. Control was treated with serum-free medium. After 48 h, cells were harvested and used for isolation of RNA. RT-PCR was performed as described in *Materials and methods*. The differential gene expressions were normalized using corresponding GAPDH expression level. The data are the means ± SE of three independent experiments. *Significantly different from control group, #significantly different from cholesterol group ($p < 0.05$)

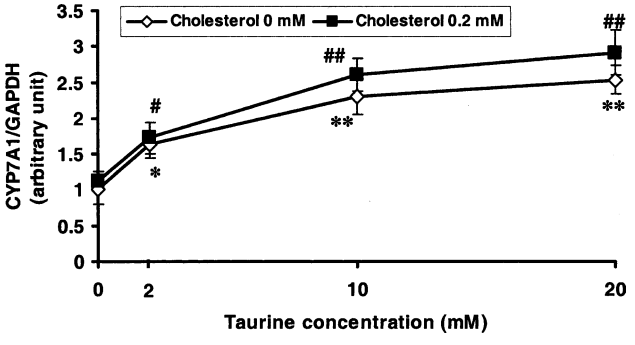

Fig. 2. Effect of dose-dependent treatment of taurine on CYP7A1 mRNA expression in Hep G2 cells. Hep G2 cells were cultured to confluence, changed into serum-free medium for 24 h, treated with taurine 0, 2, 10, 20 mM and/or cholesterol 0.2 mM. After 48 h, cells were harvested and used for isolation of RNA. Real time PCR was performed as described in *Materials and methods*. The differential gene expressions were normalized using corresponding GAPDH expression level. The data are the means ± SE of three independent experiments. $^{*}p < 0.05$, $^{**}p < 0.01$ vs. the cholesterol-free and taurine-free group; $^{\#}p < 0.05$, $^{\#\#}p < 0.01$ vs. the cholesterol 0.2 mM and taurine-free group

0, 2, 10 or 20 mM. Cholesterol in this experiment did not cause a significant effect on CYP7A1 mRNA level. In the presence of cholesterol, taurine also induced CYP7A1 gene expression (Fig. 2) in a manner similar to the effect seen with taurine alone. Although the expression of CYP7A1 gene in the case of cholesterol treatment was a little higher than the one without cholesterol treatment, there was no significant difference between them.

Effect of time-dependent treatment of taurine on CYP7A1 gene expression

A time-response study of CYP7A1 gene expression was then performed. Based on the dose-dependent experiment, a concentration of 20 mM taurine was chosen for the experiment. After achieving confluence, Hep G2 cells were treated with or without 20 mM taurine in the absence or presence of 0.2 mM cholesterol and harvested at 4, 24 or 48 hours for mRNA measurement. No significant effect was observed in control and cholesterol-treated cells. Taurine-treated cells, with or without cholesterol, at 4 hours showed a significant increase of CYP7A1 mRNA levels compared to their respective controls without taurine treatment. The expression of CYP7A1 was further induced at 24 and 48 hours of taurine treatment. No significant difference was observed between taurine-treated cells, with or without cholesterol (Fig. 3).

Effects of taurine and glycine on CYP7A1 mRNA expression

Glycine, which is a structural analogue of taurine, was used to investigate the specificity of the taurine effect

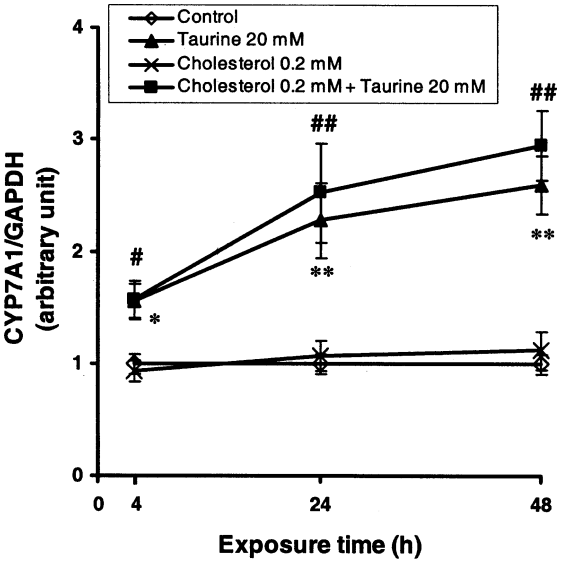

Fig. 3. Effect of time-dependent treatment of taurine on CYP7A1 mRNA expression in Hep G2 cells. Hep G2 cells were cultured to confluence, changed into serum-free medium for 24 h, treated with taurine 20 mM and/or cholesterol 0.2 mM. After 4, 24 and 48 h, cells were harvested and used for isolation of RNA. Real time PCR was performed as described in *Materials and methods*. The differential gene expressions were normalized using corresponding GAPDH expression level. The data are the means ± SE of three independent experiments. $^{*}p < 0.05$, $^{**}p < 0.01$ vs. the cholesterol-free and taurine-free group at the same time; $^{\#}p < 0.05$, $^{\#\#}p < 0.01$ vs. the cholesterol 0.2 mM and taurine-free group at the same time

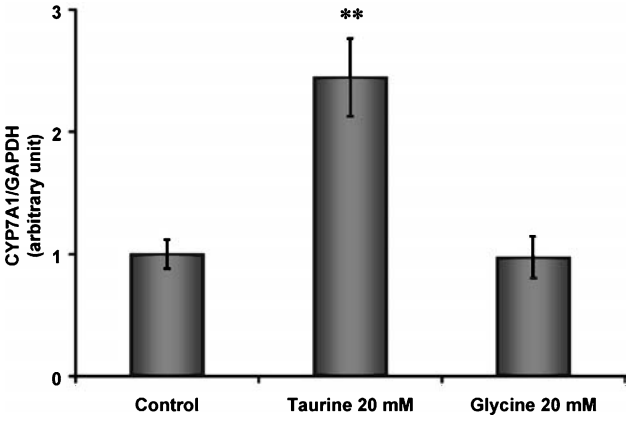

Fig. 4. Effect of taurine or glycine treatment on CYP7A1 mRNA expression in Hep G2 cells. Hep G2 cells were cultured to confluence, changed into serum-free medium for 24 h, treated with taurine 20 mM or glycine 20 mM. After 48 h, cells were harvested and used for isolation of RNA. Real time PCR was performed as described in *Materials and methods*. The differential gene expressions were normalized using corresponding GAPDH expression level. The data are the means ± SE of three independent experiments. $^{**}p < 0.01$ vs. the control group

relative to CYP7A1 gene expression. Hep G2 cells were treated with either taurine (20 mM), glycine (20 mM) or neither agent for 48 hours. Glycine failed to induce CYP7A1 mRNA levels while taurine significantly increased CYP7A1 mRNA levels (Fig. 4).

Discussion

This study shows that taurine supplementation enhanced CYP7A1 gene expression in Hep G2 cells, and this effect exhibited a characteristic dose- and time-dependent response relative to taurine treatment. These results also imply that the Hep G2 cell line may be an appropriate model for studying the effects of taurine on human cholesterol metabolism.

In *in vivo* studies, dietary taurine supplementation has been known to lower cholesterol profiles in animals and humans (Yokogoshi et al., 1999; Chen et al., 2004; Murakami et al., 2002; Cantafora, 1986; Herrmann, 1959; Zhang et al., 2004). The cholesterol-lowering effects of taurine are mainly considered to result from two sites of action. First, taurine's ability to increase the conversion of cholesterol to bile acid is due to its enhancement of CYP7A1 activity (Murakami et al., 1996), which is the first and rate-limiting enzyme for bile acid synthesis. In the other site of action, taurine can increase bile acid conjugation by elevating hepatic taurine levels, with a subsequent increase in biliary bile acid secretion (Sugiyama et al., 1989). We demonstrated that taurine increases the activity and mRNA level of CYP7A1 in rats (Yokogoshi et al., 1999).

Until now few studies have examined the effect of taurine on CYP7A1 gene expression *in vitro*. In the present study, we used Hep G2 cells, a human hepatoblastoma cell line, to investigate the effect of taurine on human CYP7A1. Although no extensive study examining the co-relationship of CYP7A1 mRNA expression between human liver and Hep G2 cell line, several agents that are known to regulate the CYP7A1 mRNA *in vivo* also regulate the mRNA in Hep G2 cells (Taniguchi et al., 1994; Charoenteeraboon et al., 2005). Our data show that taurine enhanced human CYP7A1 mRNA level. Taurine (2 mM) induced the expression of the CYP7A1 gene, with greater expression observed at the higher concentrations of 10 and 20 mM. Taurine had a similar effect when cholesterol was present in the medium. The length of taurine exposure also influenced the CYP7A1 mRNA level. After a 4 h incubation in the presence of taurine the induction of CYP7A1 mRNA expression was less than with incubations lasting either 24- and 48-h in the presence or absence of cholesterol. Glycine is a structural analogue of taurine, and in this study, it did not affect CYP7A1 gene expression in Hep G2 cell. This result implies a specific effect of taurine on CYP7A1 gene expression.

In this study, two control groups were used: one set of groups were not exposed to either cholesterol or taurine while the other group was treated cholesterol. Our data show that taurine stimulated CYP7A1 gene expression in the presence of cholesterol in the medium. This result is consistent with *in vivo* study, in which dietary cholesterol was used to induce serum cholesterol in animals (Yokogoshi et al., 2002). Taurine treatment without cholesterol in the medium also induced CYP7A1 mRNA level. It has been reported that dietary taurine, without cholesterol in the diet, may induce CYP7A1 activity in normal hamsters (Murakami, 2002). In that case, serum cholesterol was also significantly reduced in the taurine treatment group compared to the control group, with the differential pattern in hepatic cholesterol also noted between the groups. However, these responses were not reported in rats (Yokogoshi et al., 1999). The similarity between Hep G2 cells and hamsters in the response to taurine treatment may be explained in part by the similarities between human and hamster relative to cholesterol metabolism (Andersen and Cook, 1986; Horton et al., 1995). More studies may be necessary to investigate the cholesterol-lowering effect of taurine under normal conditions.

It is well documented that CYP7A1 gene expression is stimulated by dietary cholesterol in the murine (Peet et al., 1998; Torchia et al., 1996; Schwarz et al., 2001). In the report by Taniguchi et al. (1994), 25-hydroxycholesterol induced the expression of CYP7A1 gene in Hep G2 cells after 8 h (increased 18%), but by 24 h its levels had fallen below the control level (in serum-free medium). Our data also show that cholesterol addition to the medium did not have a definitive effect on CYP7A1 gene expression in Hep G2 cells, although the expression of the CYP7A1 gene was a little higher in the case of cholesterol treatment compared to the one without cholesterol treatment. The discrepancy between our results and those of Taniguchi et al. (1994) may be due to the difference in potency of cholesterol and 25-hydroxycholesterol and the doses used in the treatment. Besides that, it was reported that dietary cholesterol did not induce the human CYP7A1 transgene in mice (Agellon et al., 2002). This may be due to the lack of an LXR response element in the human CYP7A1 gene (Chiang et al., 2001). It may also explain the sensitivity of serum cholesterol to dietary cholesterol consumption in humans (Clifton et al., 1990). However, more studies may be necessary to clarify the effect of cholesterol and taurine on the expression of CYP7A1 gene, particularly when both factors are present at abundant levels in the medium.

In humans, glycine conjugates of bile acids predominate in bile. In this study, we showed that taurine, but not glycine, enhanced CYP7A1 mRNA levels. This result implies that the cholesterol-lowering effect of taurine may relate to its effect on CYP7A1 rather than its effect on bile conjugation, although the latter is still not excluded by this study. Determination of bile acid composition may be necessary to approach this question.

Induction of CYP7A1 leads to an increase in bile acid concentration in the medium. Several bile acids have been reported to suppress CYP7A1 expression in Hep G2 cells (Lew et al., 2004). In this study, the change in CYP7A1 mRNA levels from 24 h to 48 h of incubation was less steep than the change from 4 h to 24 h (Fig. 3). This response may reflect the increase of bile acid concentration in the medium. However, more studies are needed to clarify the effect of bile acid accumulation in this situation.

The mechanism of taurine's effect on CYP7A1 gene expression is still unknown. The CYP7A1 gene has been reported to be regulated at the gene transcriptional level by cholesterol, bile acids, hormones, etc. through nuclear receptors (Russell and Setchell, 1992; Chiang, 1998). The effect of taurine on these nuclear receptors should be examined, with the aim of determining its role in the regulation of the CYP7A1 gene. Based on our findings, Hep G2 cells may be an appropriate cell line for studying the molecular effects of taurine on human CYP7A1 gene expression, as well as on human cholesterol metabolism.

In conclusion, these results showed that, in agreement to previous studies using animal models, taurine induces the mRNA levels of CYP7A1 in Hep G2 cells. This activity could play a role in the conversion of cholesterol into bile acids. These results also imply that the Hep G2 cell line may be an appropriate model for studying the effects of taurine on human cholesterol metabolism.

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