REVIEW

The effect of taurine on cholesterol metabolism

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The elevated plasma cholesterol level, in particular, LDL cholesterol is regarded as an important risk factor for the development of atherosclerosis and coronary artery disease. A number of studies provide the evidence that taurine has the efficient action to reduce plasma and liver cholesterol concentrations, especially to decrease VLDL and LDL cholesterol in hypercholesterolemia animal induced by high cholesterol diet. Cholesterol lowering effect of taurine is actually involved in the regulatory mechanism of cholesterol and bile acid homeostasis that mediated by CYP7A1, which has become a biomarker for cholesterol metabolism and itself is also regulated by several factors and nuclear receptors. This review summarizes the change of cholesterol concentration in metabolism observed in feeding studies of hypercholesterolemia animal dealing with taurine, and then, addresses the possible metabolic and molecular mechanisms of cholesterol lowering effect by taurine in three aspects, cholesterol clearance from blood circulation, bioconversion of cholesterol to bile acid in liver, and excretion of cholesterol and bile acid from intestine.

Keywords:
Bile acid / Cholesterol / Cholesterol 7a-hydroxylase / Low density lipoprotein receptor / Taurine

1 Introduction

Taurine (2-aminoethanesulfonic acid), rich in sea food, is a conditionally essential amino acid which is not incorporated into proteins, but rather is found free in most mammalian tissues, such as heart, retina, liver, brain, and platelets, leukocytes [1]. It was considered as a nonessential nutrient in human beings until 1975 when it was found that formula-fed, pre-term infants were not able to sustain normal plasma or urinary taurine levels [2]. Signs of taurine deficiency have also been detected in children on long-term, total parenteral nutrition [3] and in the patients with "blind-loop" syndrome [4]. Furthermore, in vivo studies have demonstrated that low levels of taurine are associated with various pathological lesions, including cardiomyopathy, retinal degeneration, and growth retardation, etc. [5]. Now it is well known that taurine has many biological and physiological properties, such as antioxidation, osmoregulation, membrane stabilization, modulation of cellular calcium levels and serving as a neurotransmitter and neuromodulator, etc. [1, 6–9]. In lipids metabolism, the effect of taurine is considered only because of its conjugation with bile acids, which is perhaps its best-known function although that just accounts for a small proportion of total available taurine in the body [10].

A great number of studies with guinea pigs, rats, mice, and hamsters revealed that taurine affected cholesterol metabolism since Tsuji *et al.* published their research results in 1979 [11–21]. In the early feeding studies dealing with taurine, different types of hypercholesterolemia model were used, and taurine showed cholesterol lowering effect in exogenous hypercholesterolemia induced by high cholesterol diet [12, 14, 18, 19], and on the contrary, it showed cholesterol

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Abbreviations: ABCG5, ATP-binding cassette G5; **ABCG8**, ATP-binding cassette G8; **ACAT**, acyl-coenzyme A: cholesterol acyltransferase; **ApoB-100**, Apolipoprotein B-100; **ApoE**, Apolipoprotein E; **BSEP**, bile salt export pump; **BARE**, bile acid response element; **BHT**, 2,6-di-tert-2,2-butyl-p-cresol; **CYP7A1**, cholesterol 7a-hydroxylase; **FGF19/FGFR4**, fibroblast growth factor 19/fibroblast growth factor receptor 4; **FXR**, farnesoid X receptor; **HDL**, high density lipoprotein; **HMG-CoA**, 3-hydroxy-3-methyl-glutaryl coenzyme; **HNF4**α, hepatocyte nuclear factor 4α; **I-BABP**, ileal bile acids binding protein; **I-BAT**, ileal bile acids transporter; **IDL**, intermediate density lipoprotein; **LDL**, low density lipoprotein; **LDLR**, low density lipoprotein receptor; **LRH-1**, liver receptor homolog-1; **LXR-**α, liver X receptor α; **MAPK/JNK**, mitogen-activated protein kinase/Jun N-terminal kinase; **OST-**α**/OST-**β, organic solute transporter α and β heterdimer; **PAN**, puromycin aminonucleoside; **PB**, phenobarbital; **PCB**, polychlorinated biphenyl; **RXR**, retinoid X receptor; **SHP-1**, small heterodimer partner; **STZ**, streptozotocin; **TAG**, triacylglycerol; **TC**, total cholesterol; **TNF**, tumor necrosis factor; **VLDL**, very low density lipoprotein

improving effect in endogenous hypercholesterolemia caused by diabetes and some xenobiotics, etc. [13, 15–18]. These observations suggest that cholesterol lowering effect of taurine is due to the increased biotransformation of cholesterol to bile acids and the excretion of bile acids [12, 14, 15, 18], and cholesterol improving effect is due to the increased *de novo* synthesis of cholesterol [16]. As the elevated plasma cholesterol level is one of the high risk factors for the development of atherosclerosis, the cholesterol lowering effect of taurine has been studied intensively, and the possible metabolic and molecular mechanisms have also been discussed in the last two decades.

This review, first, summarizes the change of cholesterol concentration in metabolism observed in feeding studies of hypercholesterolemia animal dealing with taurine, and, second, addresses the possible metabolic and molecular mechanisms of cholesterol lowering effect by taurine.

2 The effect of taurine on serum and liver cholesterol levels in different types of hypercholesterolemia

Table 1 summarizes an overview about some published studies reporting taurine's effects on serum (or plasma) and liver total cholesterol (TC) levels in rat, mouse, hamster, and rabbit with exogenous or endogenous hypercholesterolemia.

It is evident that taurine shows cholesterol lowering effect in exogenous hypercholesterolemia rat and mouse by high cholesterol/sodium cholate diet, with the range between −22% and −67% in serum (or plasma) TC, and with the range between −26% and −42% in liver TC. In particular, high density lipoprotein (HDL)-cholesterol level changed from +11% to +43%, and very low density lipoprotein (VLDL)+low density lipoprotein (LDL)-cholesterol concentration varied from −48% to −66%. It is also observed that taurine reduces TC concentrations in serum and liver and decreases non HDL-cholesterol level in hamster [21]. These indicate that the decrease in serum (or plasma) TC level by taurine supplementation is mainly due to the decrease in VLDL and LDL cholesterol, and the effect is already clear in the condition of 1% taurine supplemented in diet with 7 days feeding. In the case of exogenous hypercholesterolemia induced by high cholesterol diet (without sodium cholate), the results are different. Serum and liver TC were decreased by taurine only marginally by approximately 3% and 5%, respectively, in rat, and decreased by 20% and 15%, respectively, in mouse; however, serum TC concentration was raised by 10% and liver TC level declined by 5% in rabbit.

In the presence of sodium cholate, high dietary cholesterol is easy to be assimilated because cholate is well known for its activity on cholesterol uptake. Therefore, most of dietary hypercholesterolemia model is induced by high cholesterol diet with sodium cholate, especially rat. It has been reported that rat is a poor model for development of experimental atherosclerosis as it is capable of facilitating disposal of excess cholesterol [22, 23]. Chen et al. [19] also reported that mouse and rat showed different responses to dietary cholesterol and sodium cholate, cholesterol degradation in rat was more susceptible and to be improved by dietary cholesterol to keep the relative stability of serum and liver TC concentrations, whereas it was more sensitive and to be repressed by cholate in mouse. Thus, cholesterol lowering effect of taurine has been consistently observed in hypercholesterolemia mouse induced by high cholesterol diet without sodium cholate, but not hypercholesterolemia rat. In 2009, Zulli et al. [24] reported that taurine has no action to reduce plasma TC concentration in rabbit fed with the diet containing 0.5% cholesterol/0.5% methionine/5% peanut oil for 4-weeks. In this study, a multiple model was made with hyperhomocysteinemia, hypermethioninemia, and hyperlipidemia to determine whether taurine could specially protect against coronary artery disease during an atherogenic diet, and taurine showed its antiatherogenic property by markedly inhibiting the increase in plasma methionine and completely inhibiting the increase in total homocysteine level, but no decline of TC or LDL concentration was observed. Balcan et al. [25] also indicated that taurine has no effect to reduce plasma and liver TC levels in atherosclerotic rabbit during regression period. The above results suggest that different species respond differently to increased cholesterol intake with elevations in blood cholesterol, and taurine may show its antiatherogenic property without having any effect on plasma lipid levels in rabbit.

Endogenous hypercholesterolemia is often caused by nephritis, hypothyroidism, diabetes, and some xenobiotics. Intraperitoneal or subcutaneous administration of puromycin aminonucleoside (PAN) to rats results in nephrosis associated hypercholesterolemia, and the reduction of plasma and liver TC levels and the increase of HDL-cholesterol by daily taurine injection were observed [13], mainly due to its therapeutic effects in attenuating PAN induced nephrotic syndrome. In the case of endogenous hypercholesterolemia induced by hypothyroidism, which is characterized by an increase of LDL- and intermediate density lipoprotein (IDL)-cholesterol caused by an enhancement of the defective receptor-mediated catabolism of lipoproteins [26], cholesterol lowering effect of taurine was not observed [15]. One of the complications in diabetes is atherosclerosis, thus it is also be concerned for the effect of taurine on cholesterol metabolism in diabetes rat. The result was observed that taurine did not decrease serum TC concentration in genetic diabetes rat fed with cholesterol-free diet, but marginally increased by 14%, whereas taurine significantly reduced serum and liver TC concentrations in genetic diabetes rat fed with high cholesterol/sodium cholate diet by 30% and 27%, respectively [18]. It has been reported that the administration of polychlorinated biphenyl (PCB), 2,6-di-tert-2,2-butyl-p-cresol (BHT), and barbital derivatives to rat caused hypercholesterolemia [16, 27, 28]. PCBs are synthetic organic compounds and harmful contaminants which are widely distributed in the environment, and PB is one of the well used sleeping drugs. Interestingly, in the case of endogenous

Table 1. Effect of taurine on TC concentrations of blood and liver as observed in studies with different hypercholesterolemia types

Species	Rat	Rat	Rat	Rat	Mouse	Mouse	Rat	Rat	Rat	Rat	Rat	Rat	Hamster	Rabbit
Hypercholesterolemia type	High cholesterol/fat/sodium cholate diet induced	High cholesterol/sodium cholate diet induced	High cholesterol/sodium cholate diet induced	High cholesterol diet induced	High cholesterol/sodium cholate diet induced	High cholesterol diet induced	Genetic diabetes induced	Genetic diabetes induced	PAN induced	Thiouracil induced	PB induced	PCB induced	High fat/cholesterol diet induced	High cholesterol/peanut oil/methionine diet induced
Taurine feeding	5% in diet	5% in diet	1% in diet	1% in diet	1% in diet	1% in diet	3% in high cholesterol diet	3% in cholesterol-free diet	500 mg/kg body weight i.p.	3% in diet	3% in diet	3% in diet	0.7% in drinking water	2.5% in diet
Feeding period (days)	21	14	7	7	7	7	14	21	10	14	10	15	28	28
Percental change of serum or palsma TC concentration (compared with control)	−67%	−42%	−42%	−3%	−22%	−20%	−30%	+14%	−13%	−2%	+5%	+36%	−14%	+10%
Percental change of serum or plasma HDL-C concentration (compared with control)	+43%	+14%	+11%	+8%	+35%	−12%	+25%	+17%	+34%	−6%	n.d.[a)]	+50%	0%	0%
Percental change of serum or plasma (VLDL+LDL)-C concentration (compared with control)	n.d.[a)]	n.d.[a)]	−66%	−15%	−48%	−26%	−54%	+9%	−20%	−16%	n.d.[a)]	+25%	−24%	n.d.[a)]
Percental change of liver TC concentration (compared with control)	−42%	−26%	−28%	−5%	−26%	−15%	−27%	−5%	−26%	−8%	+25%	+59%	−15%	n.d.[a)]
Reference	[12]	[14]	[19]	[19]	[19]	[19]	[18]	[18]	[13]	[15]	[16]	[17]	[20]	[24]

a) Not determined.

hypercholesterolemia induced by phenobarbital (PB) and PCB, taurine did not reduce serum and liver TC concentrations but caused a significant enhancement. These were mainly attributed to the stimulation of liver cholesterol synthesis, as taurine increased the conversion of [^{14}C] acetate to nonsaponifiable compounds which close related to the activity of 3-hydroxy-3-methyl-glutaryl coenzyme A (HMG-CoA) reductase [16, 17].

Although the effect of taurine on cholesterol metabolism is very different from different types of endogenous hypercholesterolemia, cholesterol lowering effect has been consistently observed in many independent experiments performed by rat and mouse with exogenous hypercholesterolemia caused by high cholesterol/sodium cholate loading diet.

3 The effect of taurine on cholesterol clearance pathway from blood circulation in hypercholesterolemia

Although cholesterol is an essential element of biological membranes, hypercholesterolemia increases the risk of developing cardiovascular diseases. In particular, LDL cholesterol is a well-established risk factor for susceptibility to atherosclerosis and coronary artery disease [29, 30]. VLDL is synthesized in the liver and secreted to the circulation to forming IDL and LDL. VLDL and LDL are removed from circulation by LDL receptor (LDLR), which binds to Apolipoprotein B-100 (ApoB-100) and Apolipoprotein E (ApoE) moieties on them. LDLR plays an important role in the regulation of plasma LDL cholesterol by mediating about two-thirds of LDL clearance from circulation [31]. Thus, VLDL secretion, plasma VLDL + LDL cholesterol, and LDLR protein level or activity are closely related, and are thought to be keeping in a dynamic equilibrium.

It has been reported by Murakami et al. [32] that taurine increased ^{125}I–labeled LDL binding to LDL receptor by 52% and 58% in hamsters fed either a normal chow or high-fat diet respectively for 14 days, and LDL kinetic analysis showed that taurine intake resulted in significant faster plasma LDL fractional catabolic rates. Their results suggest that taurine elevates hepatic LDLR activity and thereby decreases serum cholesterol level. Furthermore, in 2011, Chang et al. [21] demonstrated taurine significantly upregulated LDLR gene expressions in hamster for 4-weeks feeding with high-fat/cholesterol dietary. With taurine deficient model generated by giving mouse 0.5% guanidinoethyl sulfonate (GES) GES solution, the inhibitor of taurine transport [33], Chen et al. [34] reported that LDLR protein level was not affected by either taurine deficient or taurine supplemented, whereas triacylglycerol (TAG) secretion rate was significantly repressed by taurine supplementation. Since dietary TAG is transported in chylomicrons and endogenous TAG is transported as VLDL, and VLDL catabolism can be blocked by injection of tyloxapol, finally results in TAG accumulation in the circulation [35]. Therefore, VLDL release rate can be expressed by TAG secretion rate at a certain extent when tyloxapol is injected to animal. The above results observed in different groups indicate that taurine lowers cholesterol concentration by repressing VLDL (TAG) secretion from the liver and improves cholesterol clearance from blood circulation by upregulating LDLR binding capacity.

The liver is the organ to synthesize and secrete the apolipoproteins containing apoB-100, which is recognized by LDLR. ApoB-100 is an essential structural component of VLDL and LDL and is required for the intracellular assembly and the secretion of these lipoproteins [36]. As the elevation of the concentration of apoB-100 as well as of LDL cholesterol is also regarded as a risk factor for coronary artery disease [29, 30, 36], it is important to investigate the factors controlling the secretion rate of apoB by the liver. The study was designed by Yanagita et al. [37] to test taurine's effect on apoB-100 secretion and lipid metabolism by using the human hepatoblastoma cells HepG2, which have been found to retain many typical functions of the normal human hepatocytes including lipoprotein and apolipoprotein synthesis. Their results demonstrated taurine at the concentrations of 10^{-4} and 10^{-3} M reduced apoB-100 secretion from HepG2 cells preincubated with oleate medium in DMEM by 42% and 45%, respectively [37]. In addition, their data also indicated taurine (10^{-3} M) significantly reduced the cellular cholesterol-mass by 19% and decreased the synthesis of cholesterol ester from [^{14}C] oleic acid by 58% in the cells and reduced its secretion into medium by up to 43% [37]. It is well known that cholesterol ester formation is catalyzed by acyl-coenzyme A: cholesterol acyltransferase (ACAT) from free cholesterol and acyl-CoA. Reduction of the synthesis of cholesterol ester may suggest that relatively high amount taurine exerts for ACAT inhibitor.

The above findings reveal that taurine lowers cholesterol concentration by reducing apoB and VLDL secretion from the liver, and improving cholesterol clearance from the circulation by upregulating LDLR binding capacity led to increase of LDL uptake, and suggest indirectly that taurine accelerates the degradation of cholesterol in the liver, thus results in reduction of VLDL release to the circulation.

4 The effect of taurine on cholesterol catabolism or bile acid synthesis pathway in hypercholesterolemia

Cholesterol is an extremely important biological substance that has roles in membrane structure as well as being a precursor for the synthesis of steroid hormone and bile acid. About half of the cholesterol in the body derives from de novo biosynthesis. Except utilized in the formation of membranes and in the synthesis of steroid hormone, the greatest proportion of cholesterol from both diet and synthesis is used in conversion to bile acid in the liver. Thus, cholesterol conversion to bile acids plays a vital role for elimination of

cholesterol, which is one of the main factors regulating cholesterol homeostasis in the body [38].

Table 2 summarizes taurine's effects on bile acid synthesis in rat, mouse and hamster with hypercholesterolemia reported by several research groups. Apparently, taurine improves fecal bile acid excretion in hypercholesterolemia rat regardless of being caused by high cholesterol diet or endogenous factors such as diabetes and hypothyroidism, with the range between +24% and +75%, but not significantly affects fecal cholesterol excretion except that +16% increasing is observed in lard supplemented high cholesterol diet induced hypercholesterolemia rat. In the case of hypercholesterolemia mouse led by cholesterol or cholesterol/sodium cholate loading diet, +16% enhancement of fecal bile acid excretion is observed, and the change of fecal cholesterol is not observed. In hypercholesterolemia hamster induced by high fat/cholesterol diet, fecal bile acid and cholesterol level increased +35% and +19% respectively by taurine.

There are two pathways in bile acid biosynthesis, one is the classic (also known as neutral) pathway which is the main pathway in the conversion of cholesterol to bile acid, and the other is alternative (also known as acidic or mitochondrial) pathway. Cholesterol 7a-hydroxylase (CYP7A1) is the rate-limiting enzyme in the classic pathway [39, 40]. In Table 2, it is evident that taurine remarkably increases CYP7A1 activity with the range between +82% and +151%, and improves CYP7A1 mRNA level with the range between +95% and +119% in hypercholesterolemia rat and mouse caused by high cholesterol/sodium cholate diet. About +30% elevation of CYP7A1 activity and +63% enhancement of CYP7A1 mRNA expression are observed in hypercholesterolemia rat and hamster, respectively, which induced by high cholesterol/fat diet, and no improvements of activity and mRNA level of CYP7A1 are observed in hypercholesterolemia mouse led by high cholesterol diet without sodium cholate.

The above studies reveal that cholesterol-lowering effect of taurine is carried out by enhancing CYP7A1 activity or mRNA expression and fecal bile acid excretion in hypercholesterolemia hamster and rat with high cholesterol/fat diet and in hypercholesterolemia rat and mouse with high cholesterol/sodium cholate diet. Interestingly taurine does not improve CYP7A1 activity /or mRNA expression in hypercholesterolemia mouse by cholesterol diet without sodium cholate. Chen et al. [19] reported there was an apparent difference in the regulation of cholesterol degradation or bile acid biosynthesis between mice and rats, the diet rich in cholesterol induced CYP7A1 mRNA expression in rats (but not in mice), and CYP7A1 mRNA level was significantly repressed by diet high in combination of cholesterol and sodium cholate, but still notably higher than that of the rats with normal chows. In mice, CYP7A1 mRNA level was marginally increased by the diet rich in cholesterol, and markedly decreased by adding sodium cholate to cholesterol diet, even far less than that of the mice with normal chows [19]. Boone et al. [41] also reported that western blotting analysis showed dietary cholesterol significantly increases CYP7A1 protein levels in rats but not in mice. Other reports [42, 43] showed that dietary cholesterol may act to increase or decrease CYP7A1 mRNA levels in C57BL/6J mice depending on the type of fat added to the diet, and olive oil supplement caused increased expression of CYP7A1. These studies suggest there is considerable variation among animals in terms of their responses to consumption of excess dietary cholesterol. Hamsters and mice are not resistant to dietary cholesterol and exhibit marked elevations in serum cholesterol level when given diets supplemented with cholesterol, whereas rats show very little increase in serum cholesterol level when given a similar cholesterol challenge [44, 45]. According to Chen's paper, taurine induced CYP7A1 expression only in the present of sodium cholate in high cholesterol diet, subsequently showed its more efficient cholesterol lowering effect in rat and mouse [19], although they displayed different response to dietary cholesterol. In addition, in vitro study reported by Lam et al. [46] demonstrated taurine remarkably induced CYP7A1 expression in HepG2 cells with time- and dose-dependent in the presence of cholesterol in medium. This paper also suggests Hep G2 cell line may be an appropriate model to study the effects of taurine on human cholesterol metabolism [46].

Cholesterol degradation or bile acid biosynthesis is critically regulated in order to maintain cholesterol or bile acid homeostasis in the body. CYP7A1, the rate-limiting enzyme in the classic pathway of bile acid biosynthesis [39], has been widely reported to being regulated by several nuclear receptors at the level of gene transcription to balance the elimination of cholesterol responsive to the physiological status in the body [47, 48]. Two regions for transcription factor binding (bile acid response element-I (BARE-I) and BARE-II) have been identified in the CYP7A1 promoter [49]. BARE-I in mouse binds liver X receptor α (LXRα), a nuclear receptor identified as a positive regulator of CYP7A1 transcription [50, 51], whereas LXRα binding site is not present in the CYP7A1 gene in human [52]. The ligands that activate LXRα are oxysterols [53], which increaseed after cholesterol feeding. BARE-II contains binding regions for hepatocyte nuclear factor 4α (HNF-4α) and liver receptor homolog-1 (LRH-1), which were reported to be essential for basal level expression of CYP7A1 [54, 55]. Farnesoid X receptor (FXR), a bile acid receptor, plays a critical role in the regulation of bile acid synthesis and homeostasis. FXR represses CYP7A1 transcription by promoting the transcription of the atypical nuclear receptor small heterodimer partner (SHP-1), which interacts with HNF4α and LRH-1 and then suppresses CYP7A1 gene transcription [56, 57]. Bile acids such as lithocholic acid, chenodeoxycholic acid, and deoxycholic acid are ligands that activate FXR. Although studies in CV-1 cells did not show cholic acid had strong affinity to activate FXR [48], it has been demonstrated in mice that cholic acid was a powerful activating ligand for FXR in vivo [58]. These findings support the idea that bile acid pool size and components proportion are responsible for inhibition of CYP7A1 by providing additional activating ligands to activate FXR, the negative regulator of CYP7A1.

Table 2. Effect of taurine on fecal excretion of bile acid and steroid, and CYP7A1 activity and mRNA level as observed in studies with hypercholesterolemia animal model

Species	Hypercholesterolemia type	Taurine feeding	Feeding period (days)	Percental change of fecal bile acid concentration (compared with control)	Percental change of fecal neutral steroid or fecal cholesterol concentration (compared with control)	Percental change of CYP7A1 activity (compared with control)	Percental change of CYP7A1 mRNA (compared with control)	Reference
Hamster	High fat/cholesterol diet induced	0.7% in drinking water	28	+35%	+19%	n.d.[a)]	+63%	[20]
Rat	High cholesterol/lard/sodium cholate diet induced	5% in diet	21	+75%	−6%	+151%	n.d.[a)]	[12]
Rat	High cholesterol/sodium cholate diet induced	5% in diet	14	+60%	5%	n.d.[a)]	+95%	[14]
Rat	High cholesterol/lard diet induced	1% in diet	7	+46%	+16%	+30%	n.d.[a)]	[68]
Rat	High cholesterol/sodium cholate diet induced	5% in diet	14	+59%	+5%	n.d.[a)]	+95%	[68]
Mouse	High cholesterol diet induced	1% in diet	7	+16%	+4%	−4%	−4%	[19, 59]
Mouse	High cholesterol/sodium cholate diet induced	1% in diet	7	+16%	−2%	+82%	+119%	[19, 59]
Rat	High cholesterol/sodium cholate diet induced (STZ-induced Diabetic rats)	5% in diet	14	n.d.[a)]	n.d.[a)]	n.d.[a)]	+98%	[69]
Rat	High cholesterol/sodium cholate diet induced (Genetic Diabetic rats)	3% in diet	14	+42%	n.d.[a)]	n.d.[a)]	n.d.[a)]	[18]
Rat	Cholesterol-free diet (Genetic Diabetic rats)	3% in diet	21	+49%	n.d.[a)]	n.d.[a)]	n.d.[a)]	[18]
Rat	Thiouracil induced	3% in diet	14	+24%	+12%	n.d.[a)]	n.d.[a)]	[15]

a) Not determined.

Molecular mechanism of CYP7A1 induction by taurine is rarely discussed although its regulation pathway and relative nuclear receptors and factors have been studied extensively. In 2006, Lam et al. [59] reported that C57BL/6 mice were fed with cholesterol or cholesterol/sodium cholate diet supplemented taurine for 1 week in their experiment, and mRNA levels of CYP7A1, LXRα, HNF-4α, LRH -1, FXR, and SHP were determined. Their results showed no alternation in the mRNA levels of nuclear receptors were observed by diet treatment, although the mRNA level of CYP7A1 was significantly decreased by cholesterol/sodium cholate diet (but not by cholesterol diet) and then two-fold increased by taurine supplementation [59]. Their results suggest (1) although there are no changes on mRNA level, FXR is indeed activated by sodium cholate diet and then functions as a down-regulator to CYP7A1; (2) taurine may interrupt the activation of FXR via any unknown pathway, in spite of enhancement synthesis of bile acid, which is the activating ligand for FXR; and (3) taurine also may activate LXRα, HNF4α or LRH-1 by any indirect route because it is not a probable ligand for LXRα [59].

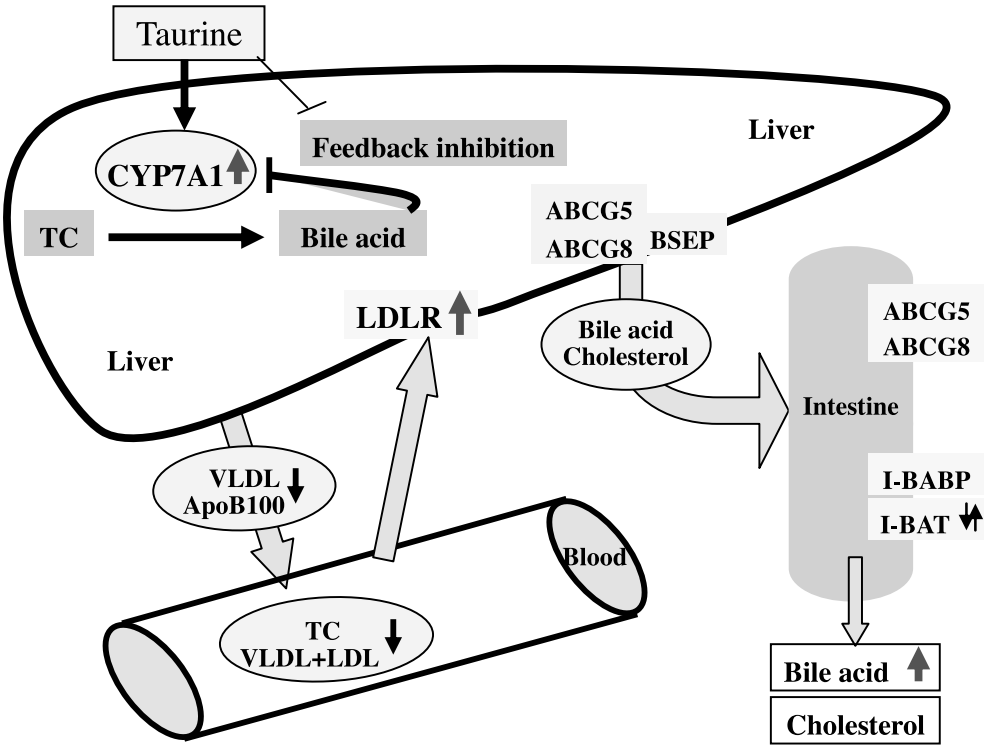

Figure 1. Proposed model explaining cholesterol lowering effect of taurine. Reduction of serum (or plasma) TC concentration by taurine is mainly due to the decrease in VLDL and LDL cholesterol. First, taurine reduces apoB and VLDL secretion from the liver, and improves cholesterol clearance from blood circulation by upregulating LDLR binding capacity led to increase of LDL uptake; second, taurine activates bioconversion of cholesterol to bile acid via enhancing CYP7A1 activity or mRNA expression, and may also interrupt the feedback inhibition of bile acid to CYP7A1 by repressing the activation of FXR, a negative regulator of CYP7A1; third, taurine increases excretion of fecal bile acid, and possibly improves and represses I-BAT expression in different feeding situations, to affect re-absorption of bile acid from enterohepatic circulation; and fourth, taurine do not affect fecal cholesterol excretion mediated by ABCG5 and ABCG8. ABCG5/8, ATP-binding cassette G5/8; BSEP, bile salt export pump; CYP7A1, cholesterol 7a-hydroxylase; FXR, farnesoid X receptor; I-BABP, ileal bile acids binding protein; I-BAT, ileal bile acids transporter; LDL, low density lipoprotein; LDLR, low density lipoprotein receptor; TC, total cholesterol; VLDL, very low density lipoprotein.

The exact mechanism of upregulating effect of CYP7A1 by taurine remains unclear at present.

5 The effect of taurine on cholesterol excretion and bile acid re-absorption in hypercholesterolemia

Decrease of *de novo* synthesis, increase of degradation and large excretion of cholesterol are three auto-regulation mechanisms to maintain cholesterol homeostasis when high cholesterol is present in the diet. Except the excretion, degradation of cholesterol by taurine has been discussed, and *de novo* synthesis is not under consideration as being interrupted by high cholesterol diet. ATP-binding cassette G5 (ABCG5) ABCG5 and ATP-binding cassette G8 (ABCG8) ABCG8, exist in the hepatocytes and enterocytes, are induced by LXRα to enhance cholesterol efflux into biliary ducts and intestinal lumen [60]. Significant evidence indicates that deletion of ABCG5 and ABCG8 in mice leads to a marked decrease (90%) in biliary cholesterol [61], and furthermore, cholesterol secretion is linearly correlated with the gene copy number of *Abcg5/Abcg8* in mice [62].

The three important sides in bile acid homeostasis in the body are biosynthesis, excretion to feces, and re-absorption from the ileum. Besides re-absorption, the other two points have been demonstrated to be increased by taurine. Conjugated bile acids are secreted into bile by canalicular bile salt export pump (BSEP) and stored in the gallbladder and then emptied into the intestinal tract after meal. When passing through the intestinal tract, most bile acids (95%) are re-absorbed in the ileum by apical sodium-dependent bile acid transporter (also known as ileal bile acids transporter (I-BAT)) located in the brush border membrane, and transdiffused across the enterocyte to the basolateral membrane where organic solute transporter α and β heterodimer (OSTα/OSTβ) discharges bile acids into portal blood circulation, and finally taken up into hepatocytes to complete enterohepatic circulation [63]. BSEP is FXR target gene, which is the driving force for bile formation [64]. FXR induces I-BAT expression

in mouse and inhibits I-BAT expression in rabbit but does not affect I-BAT in human [65]. FXR also induces the expression of ileal bile acids binding protein (I-BABP), which is the first target gene of FXR identified in the gastrointestine system and may bind bile acids and reduce intracellular bile acid concentrations in the ileum [66].

Few studies revealed taurine's effects on cholesterol excretion and bile acid re-absorption in hypercholesterolemia. Lam et al. [59] reported the effect of taurine on some factors involved in cholesterol and bile acid homeostasis in mice. In their experiments, mRNA levels of liver ABCG5 and ABCG8 were increased by high cholesterol diet, and further improved by high cholesterol/sodium cholate diet, but not mediated by taurine. Expression of liver BSEP and jejunum ABCG5 and ABCG8 were induced by both of high cholesterol and high cholesterol/sodium cholate diets, and also not regulated by taurine. These data suggest that taurine supplementation do not affect not only the excretion of cholesterol and bile acids from the liver to bile, but also cholesterol excretion from the intestine. These are well consistent with their results of unchanged fecal neutral sterol excretion by taurine. In enterohepatic circulation of bile acid, mRNA level of I-BABP was not affected by the diets, whereas I-BAT was notably reduced by both of high cholesterol and high cholesterol/sodium cholate diets. The interesting is a reduced and an induced I-BAT expression was observed by taurine supplemented high cholesterol diet and high cholesterol/sodium diet, respectively. According to the results of fecal bile acid excretion and I-BAT mRNA level, it is conceivable that taurine lowers serum and liver cholesterol concentrations through improving excretion and suppressing re-absorption of bile acids when taking high cholesterol diet without exogenous sodium cholate, because both of expression and activity of CYP7A1 were not improved in this case. On the contrary, taurine has no effect on repressing bile acid re-absorption but notably improved CYP7A1 mRNA level in the case of sodium cholate added cholesterol feeding. These suggest that taurine may deregulate the feedback inhibition of bile acids to CYP7A1 gene expression under this special physiological condition although the mechanism is unknown at present.

6 Conclusions and future perspectives

The obvious reduction of serum (or plasma) and liver TC concentrations by taurine are the most striking observation from a number of feeding experiments with cholesterol/cholate loading diets. The decrease in serum (or plasma) TC level by taurine supplementation was mainly due to the decrease in VLDL and LDL cholesterol. Mechanistic studies dealing with this topic indicate that these effects of taurine are mediated by improved LDLR binding capacity, reduction of VLDL and apoB-100 secretion from the liver, and activated bioconversion of cholesterol to bile acid via upregulating CYP7A1, and consequently, increased excretion of fecal bile acid, and a possible improved and repressed I-BAT expression in different feeding situations that related to re-absorption of bile acid from enterohepatic circulation. The comprehensive mode of action of taurine is shown in Fig. 1.

Regulation of bile acid synthesis has been extensively studied, and CYP7A1 mRNA expression is a biomarker for studying cholesterol metabolism in animal models of hypercholesterolemia. Mouse and rat models are widely used; however, some differences exist in bile acid synthesis and regulation when they were given by cholesterol challenge with or without sodium cholate. CYP7A1 expression is markedly induced by taurine in both of rat and mouse fed with cholate-containing cholesterol diet. The action mechanism of taurine to relieve the feedback inhibition of CYP7A1 transcription by bile acid remains to be further elucidated, such as FXR-dependent pathway including FXR/SHP and FXR/fibroblast growth factor 19/fibroblast growth factor receptor 4 (FXR/FGF19/FGFR4) pathway, and FXR-independent pathway including tumor necrosis factor (TNF) receptor and mitogen-activated protein kinase/Jun N-terminal kinase (MAPK/JNK) pathway, etc. Moreover, a study provided evidence that FXR-mediated repression of bile acid synthesis requires the complementary actions of FXR in both liver and intestine [67].

Somehow, cholesterol lowering action of taurine indicates that taurine may be important during states with high dietary cholesterol habits or where cholesterol metabolism is disturbed.

The authors have declared that they have no conflict of interest.

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