

## Taurine synthesis in teleost-importance of cysteamine pathway

Yutaka Haga, Maria Mojena Gonzales, Tomoko Itoh, Hidehiro Kondo,

Ikuo Hirono, Shuichi Satoh

Tokyo University of Marine Science and Technology, Konan, Minato 4-5-7, Tokyo 108-8477,

Japan, E-mail: haga@kaiyodai.ac.jp

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### Abstract

Taurine plays various roles in animals such as growth promotion, osmoregulation, bile acid conjugation, neurotransmission, cardiac muscle contraction, antioxidant activity, and reproduction. Taurine is one of the essential nutrients for marine fish larvae and in fishes which lack endogenous taurine production. Taurine is synthesized from methionine via cysteine. Cysteine is converted to cysteine sulfinic acid by activity of cysteine dioxygenase (CDO) and cysteine sulfinic acid is converted into hypotaurine by cysteine sulfinic acid decarboxylase (CSD) in CSD pathway which is considered to be a major taurine production pathway in fish. Hypotaurine is finally converted into taurine by auto-oxidation. In addition to CSD pathway, there is two other taurine synthetic pathways are known: cysteic acid pathway where cysteine is oxidized into cysteic acid, and it is directly converted into taurine by cysteic acid decarboxylase (CAD) activity and cysteamine pathway where cysteine is converted into cysteamine and it is converted into hypotaurine by cysteamine dioxygenase (ADO). However, detail on taurine production by these two pathways is not understood.

Common carp is widely cultured in the world and world production of cypriniforms is highest among food fish species. Rainbow trout is known to have sufficient CSD activity to produce taurine via methionine. In contrast, it was reported that CSD activity in common carp is about half of that reported in rainbow trout. However, common carp did not show growth retardation when it was fed taurine deficient diet. These observations led

hypothesis that common carp is able to produce sufficient amount of taurine beside the CSD pathway. The purpose of the present study is to investigate effect of dietary supplementation of cysteine, cysteamine, methionine, and taurine on the growth, sulfur amino acid content, and gene expression of taurine synthesizing enzymes.

Eight different diets supplemented with taurine, methionine, cysteine, and cysteamine were fed to the juvenile common carps for 30 days. For control, a diet without supplying sulfur amino acid was fed. Feeding diets supplemented sulfur amino acid resulted in better survival, growth, feed conversion ratio, and protein efficiency ratio except treatments supplemented with cysteamine. It was observed that the supplementation of dietary cysteamine caused growth retardation, myopathy, and body deformity in common carp. All sulfur amino acids increased taurine deposition in the carcass and 1.5% cysteamine increased taurine deposition by 1.8 and 5.5 times higher than those of the methionine and cysteine treatments. CDO was tended to be down-regulated by cysteine and low dose of taurine but up-regulated by a high dose of cysteamine. It was observed that CSD was down-regulated by sulfur amino acids. ADO was down-regulated by methionine, cysteine and low dose of taurine but up-regulated by cysteamine.

These results suggest that CSD pathway plays a role in taurine synthesis and cysteamine pathway is another major taurine synthesizing pathway in common carp.

**Keywords:** Taurine, Synthesis, Teleosts

## Introduction

World population increase and food crisis has been warned to occur in near future. Contrast to stable production in capture fisheries without increase, world aquaculture production has increased about twice in the last decades and occupies 47% of total fishery production (FAO 2016). Fish requires relatively higher dietary protein than terrestrial animals and fishmeal is the main protein source in fish feed. Major fishmeal producer in the world is Chile and Peru. However, in order to save natural fish resources, development of fish meal free diet has been a subject for achieving sustainable aquaculture industry for next generation. Currently, fishmeal free diet can be used for laboratory experiment but supplementation of important nutrients such as taurine is essential.

Taurine plays various roles in growth, vision, reproduction, neurotransmission, osmoregulation, and antioxidant mechanism in fish (Takeuchi 2014). Although it was reported low taurine biosynthetic ability in marine carnivorous fish species, we have successfully isolated cysteine sulfonate decarboxylase, which is considered to be the rate limiting enzyme of taurine synthesis, from marine fishes such as red sea bream *Pagrus major* and yellowtail *Seriola quinqueradiata* (Haga *et al.* 2015). Detailed analysis of modulation of gene expression of CSD genes could lead development of technique to enhance taurine biosynthetic ability in fish. This paper reviews recent finding on taurine function in fish. Although detailed description on taurine transporter was not made in this paper, readers should refer appropriate reviews that published previously (Warskulat *et al.* 2007; Han *et al.* 2006; Xu *et al.* 2015).

## 1. Chemical aspect of taurine

IUPAC name of taurine is 2-ethanesulfonic acid and its molecular weight is 125.12. Taurine crystal is white spindle shape. Definition of amino acid is that the chemical has to have carboxylic acid as well as amino group in its molecule. Taurine molecule has sulfonic acid instead of carboxylic acid. So taurine is amino acid related compound but not true amino acid. Taurine is rich in fish and shellfish, aquatic reptile, cardiac muscle of animals, colostrum of humans (Jacobsen and Smith 1968; Murakoshi and Hatanaka 1977; Ozawa *et al.* 1984; Suyama *et al.*, 1979). Taurine is not included in higher terrestrial plants (Jacobsen and Smith 1968). Taurine has been isolated from bovine liver for human use.

## 2. Taurine content in aquatic organisms and tissue distribution

Aquatic organisms contains high amount of taurine and its related compounds (Table 1). Ozawa *et al.* (1984) examined taurine content in muscle of more than 50 species and found 11-356 mg/g taurine. Ohyama *et al.* (1991) also examined more than 11 fish species and 10 cephalopod, shellfish, crustacean and algae and found relatively high in muscle of tilefish, barracuda and Japanese anchovy (256-373mg/100g), and around 100-200 mg/ 100 g in other fish species. In addition, 182-1232 g/100mg, 43-75mg/100g and 21-1380mg/100g of taurine was recorded in cephalopod, shrimp, and shellfish respectively. Hiraoka *et al.* (2011) also examined taurine content in 26 fish species and found 15-1265 mg/100 g in tissue and high taurine reported in dark muscles of tuna and amberjacks (451-1265mg/100g) as well as in cephalopod (497-1031mg/100g). Taurine abundantly presents in liver (hepatopancreas),

kidney, dark muscle and gonad (Murakoshi and Hatanaka 1977; Ozawa *et al.* 1984; Sakaguchi and Murata 1987; Suyama *et al.*, 1979). Relatively high level of taurine was also detected in muscle of freshwater turtle (88-134mg/100g) (Suyama *et al.*, 1979). However, it was reported that elevation of taurine content in tuna meat after 72h during cold storage (Shiraita *et al.* 2012). So readers should keep in mind that reported taurine content in fish can be affected by changes after storage. Among prey organisms used for juvenile production in hatchery, taurine was rarely found in rotifer (80-180 mg/100 g) but considerable level of taurine was reported in *Artemia* (400-800 mg/ 100 g) with difference between strains (*A. franciscana*; 463 mg/100g, *A. tibetiana* 632 mg/100mg) (Kurihara 2008; Takeuchi 2014). Although large variation was found in taurine levels in wild zooplanktons depending on nutritional condition, 800-1200 mg/100 g of taurine was reported (Matsunari *et al.* 2003). Highest level of taurine was found in mysids among feed items used in aquaculture (2900mg/100g, Seikai *et al.* 1997). Red algae is known as rich in taurine derivatives; taurine, N-methyltaurine, N, N-dimethyltaurine, and N, N, N-trimethyltaurine were reported (Impellizzeri *et al.* 1975; Lindberg 1955; Ito 1965). D-Glycerotaurine was isolated from suginori *Gigartina leptorhynchos* and okitsunori *Gymnogongrus flabelliformis*. D-cysteinolic acid was found in algae *Polysiphonia fastigata*, sardine *Sardinopus melanostica* (Satake *et al.*, 1987), and starfish *Asteria Pectinifera* (Yoneda and Yoshimura, 1965).

Taurine content does not decrease in early embryogenesis but quickly decreases during ontogeny of Japanese flounder and yellowtail after hatching (Matsunari *et al.* 2003; Takahashi *et al.* 2005; Takeuchi *et al.* 2001). Comparing taurine content in wild and cultured yellowtail juveniles suggest that considerably lower taurine content was found in cultured

yellowtail than wild juvenile and suggested that taurine deficiency in cultured yellowtail juveniles (Matsunari *et al.* 2003). Higher taurine content in wild fish than cultured fish was also reported in Japanese flounder, red sea bream, and four-spine sculpin (Kim *et al.* 2000; Morishita *et al.* 1989; Iwatani *et al.* 2012). This kind of low taurine content in cultured fish was able to be improved by feeding zooplanktons enriched with taurine (Takeuchi 2014) and several taurine enrichment products have been commercially available in Japan. It was suggested that taurine content in fish is not only affected by dietary taurine intake (Matsunari *et al.* 2008; Takahashi *et al.* 2005) but also dietary protein in rainbow trout (Yamamoto *et al.* 2000).

### 3. Taurine synthetic pathway in animals

Taurine was synthesized from methionine and cysteine in animal body. Methionine is converted into cystathionine via homocysteine with the aid of cystathionine beta synthetase (CBS). Cystathionine is converted into cysteine by cystathionine gamma lyase. There are three taurine synthetic pathways are proposed; cysteine sulfinic acid decarboxylase (CSD) pathway, cysteamine pathway, and cysteic acid pathway. In CSD pathway, cysteine was converted to cysteine sulfinic acid by cysteine dioxygenase (CDO) and then cysteine sulfonate is decarboxylated to hypotaurine with activity of CSD. Hypotaurine is converted into taurine by auto-oxidation. CDO requires  $\text{Fe}^{2+}$  for maximum activity of 25000 Da and inactivated with chelate agent such as EDTA. On the other hand, CSD from red sea bream, yellowtail and Japanese flounder possesses NPHK motif in its primary sequence of enzyme protein and suggested to require vitamin B6 for maximum activity (Haga *et al.* 2015; Wang *et al.* 2016).

Hypotaurine is converted into taurine without aid of enzyme activity, rate limiting step of taurine production by CSD pathway is that conversion of cysteine sulfinic acid into hypotaurine. Therefore, CSD activity seems key regulator of taurine production in animal body except for two other taurine synthetic pathways. Cysteine is also important because it has biological activity as a precursor of cysteine sulfinic acid. Cysteine dioxygenase (CDO) is responsible for conversion of cysteine into cysteine sulfinic acid and CDO knockout mice exhibit severe taurine deficient syndrome even if these mice possess CSD activity (Ueki *et al.* 2011). Further, since CDO strongly expresses in placenta of human, although CSD is indispensable for taurine synthesis in humans, it was estimated that CDO primarily determines taurine status in body of mouse and human.

It was suggested that rat CSD not only play a role in decarboxylation of cysteine sulfonate but also decarboxylation of cysteine acid (Jacobsen and Smith 1968). In red sea bream, elevation of supplemental cysteine sulfinic acid under the presence of cysteic acid leads decrease of taurine produced from cysteic acid, suggesting CSD from red sea bream also recognize and convert cysteic acid as well as cysteine sulfonic acid as a substrate (Goto *et al.* 2003). In contrast, glutamic acid decarboxylase-like enzyme 1 (GADL1) which is only found in amphibian, avian, and mammals is known to function not only in decarboxylation of glutamic acid but also taurine synthesis (Liu *et al.* 2012; Winge *et al.* 2015). Hence, it was reported that mammalian GADL1 is responsible for conversion of aspartic acid into  $\beta$ -alanine and it also convert cysteine sulfinic acid and cysteic acid into hypotaurine and taurine, respectively (Liu *et al.* 2012). We isolated full length primary sequence of cysteine sulfinic acid decarboxylase from red sea bream and yellowtail and found that high expression was

commonly found in liver and pylorus in red sea bream, Japanese seabass, spotted halibut and yellowtail, suggesting CSD plays a role in taurine production in these tissues in fishes. Wang *et al* (2016) examined CDO and CSD in Japanese flounder and rainbow trout. They found that CDO expression was downregulated by taurine supplementation in rainbow trout, suggesting CDO plays a role in maintain taurine level in fish body (Wang *et al.* 2016). On the other hand, CSD but not CDO expression was downregulated in Japanese flounder (Wang *et al.* 2016). In addition, zebrafish CSD was regulated by dietary taurine level (Chang *et al.* 2013). These findings suggest that rate limiting step taurine production by CSD pathway is different depending on fish species. In turbot *Psetta maxima*, cysteine and methionine elevated level of CDO transcript (Wang *et al.* 2014). Common carp was reported to possess CDO1 and 2 and CSD, yeast hybrid expressed fusion protein of CDO1 or 2 with CSD resulted in higher taurine production potency was seen in CDO1/CSD fusion protein, suggesting CDO1 has more higher catalytic activity (Honjoh *et al.* 2009).

Taurine transporter 1-3 play a role in taurine intake in cell and presence of TauT3 paralog in fish was suggested. Mobilization of taurine by GABA transporter was also suggested and some papers suggested that GABA transporter is more important than TauT in taurine intake in cell (Liu *et al.* 1993; Zou *et al.* 2012). However, there is few report on taurine transport by GABA transporter in fish.

#### 4. Function of taurine in fish

Taurine plays a role in bile acid conjugation and excretion, lipid absorption, skin development, vision, swimming and feeding activity, reproduction, growth and development of early stage, stress response, and taste of fillet in fish.

Taurine conjugates bile salt. Glycine also does but taurine conjugated bile salt has more potent in solubility in water. Selectivity of organic acid for bile salt conjugation is diverse in teleostean species (Hagey *et al.* 2010). In carp, cyprinol sulfate, causing food poisoning toxin for carp consumer, is a main bile acid conjugate and occupies more than 94% in total bile acid (Yeh and Hwang 2001). On the other hand, taurocholic and taurodeoxycholic acids are the major bile acid constituents in Japanese flounder (Goto *et al.* 1996). Bile pigment is originated from hemoglobin in blood and blood cell has shortest biological half-life in cell of animal body. Therefore, degraded hemoglobin gives rise bililvin and bilibergin that have to be conjugated by taurine for excretion. Because water solubility of these pigments is conferred by conjugation with taurine, taurine deficiency causes abnormal accumulation of pigments and malfunction of liver and eventually led mortality. The fact that fish highly depends on taurine for bile conjugation has higher risk of taurine deficiency since they has to always consume a certain amount of taurine for maintenance of normal function of liver. Conversely, taurine deficiency seems to less occur in fishes that are able to use other organic acid for bile conjugation even when they fed low taurine diet such as plant protein based diet. Dietary intake of taurine is controlled by taurine level in a diet as well as food intake of fish. Therefore, risk of taurine deficiency is higher in winter when feed intake decreases. In fish farming site, water temperature and feed intake should be carefully observed when one

consider risk of taurine deficiency. Red sea bream requires dietary taurine when fed low fishmeal diet but its requirement in the fish is lower than yellowtail (Takagi *et al.* 2011).

Blighter skin color was reported in red sea bream fed casein based diet supplemented with taurine (Takeuchi 2014). It was reported that taurine supplementation on fishmeal based diet enhanced skin thickness and improved occurrence of scale detaching at harvesting fish (Kato *et al.* 2012; 2014). This observation was also reproduced when fish was fed moist pellet formulated with low level of fishmeal (30%) and skin thickness became 80 to 120  $\mu$ m by dietary taurine supplementation at high water temperature. However, they failed to observe effect of taurine on skin thickness at the season with low water temperature. It was probably because lower level of feed intake in cold season compared to high water season. Taurine is one of the popular components of hair treatment detergent for humans and hair growth promotion was reported by taurine supplementation. Taurine seems to promote growth of skin and its appendages in vertebrates.

Improvement of reproductive performance and larger size eggs were reported in yellowtail (Matunari *et al.* 2008). Similar improvement of reproductive performance and enhanced survival after hatching were reported in tilapia (Al-Feky *et al.* 2016). Higher taurine content in fertilized egg than unfertilized egg was found in swimming crab and elevation of taurine content was observed before hatching (Paneflorida 2004). In addition, comparing 20,000 transcripts from bloodstock with better reproductive performance (survival was less than 84% at seven days post fertilization) and worse bloodstock (survival was less than 6% at seven days post-fertilization) revealed that one of the transcripts with significant difference was CSE which is cysteine synthetic enzyme gene (Rise *et al.* 2014). These results suggest

that taurine and its precursor are important for reproduction success and early survival of embryos.

Improvement of feeding behavior was reported in red sea bream juveniles fed taurine supplemented casein based diet (Matsunari *et al.* 2008). Faster swimming speed toward tank bottom was observed immediately after completion of feeding in flounder juveniles (Kim *et al.* 2005). In addition, improvement of survival after releasing in wild environment was observed in Japanese flounder fed taurine supplemented diet (Morita *et al.* 2011). Taurine is one of the important energy source for early stages of fish (Ronnestad *et al.* 2003). In mammals, taurine occupies more than 50% of total free amino acid in eye ball and cardiac tissue. More than 70% of total free amino acid was reported to be occupied by taurine in heart ventricle in Pacific bluefin tuna (Ishihara *et al.* 2013). Reduction of plasma taurine and cysteine was reported in rat after 8 weeks of exercise (Gaume *et al.* 2005). Taurine deficiency in cardiac and skeletal muscle in fish could hinder normal function of these locomotive organs resulted in lower swimming performance of fish.

Importance of taurine in stress response has been suggested by studies in mammals. Taurine plays a role in removal of reactive oxygen species. When gilthead seabream *Sparus aurata* was exposed to confinement stress, 202 gene transcripts responded; among them, CBS and CDO responded in phase 1 when energy metabolism was reconstructed for acute response, and CSE responded in phase 3 when reconstruction of cellular homeostasis for selective classification and destruction of reactive oxygen species (Calduch-Giner *et al.* 2010). CBS expresses in central nervous system of chinook salmon, common carp, and zebrafish as a source of H<sub>2</sub>S (Pushchina *et al.* 2011; Porteus *et al.* 2014), Cells with H<sub>2</sub>S suggested to be involved in enhancement of respiratory volume as a sensor of low oxygen condition

(Pushchina *et al.* 2011). These findings suggest that synthesis of taurine precursor enhanced at stressed condition and serves as a source of H<sub>2</sub>S which act as signaling molecule.

Taurine is also suggested to affect taste of fillet of fish. When panellers sampled fillet of yellowtail *S. quinquerediata* fed a diet supplemented taurine for 18 weeks, there was no difference in taste of fillet from fish fed taurine supplemented diet and a diet formulated with 60% fishmeal but lower score was obtained for fillet from the abdominal part of fish fed low fish meal diet than taurine supplemented diet (Khaoian *et al.* 2014). There is also no effect on selection of choice “like” or “dislike” when the fillet was tasted with or without soy source (Khaoian *et al.* 2014). In addition, similar trial was also made in yearling greater amberjack *Seriola dumerili*. Extruded pellet with a low fishmeal diet was formulated with soy protein concentrate, soybean meal, and corn gluten meal. Fillet samples was tested after feeding the low fishmeal diet (10-30%) with or without 0.2-0.4% taurine for 114 days and highest score was obtained in fillet from fish fed a low fishmeal diet with 0.4% taurine was recorded (Maeno *et al.* 2012). Collectively, these reports suggest that taurine supplementation could affect on taste of fillet of fish.

Although there is few report on taurine function in invertebrates, feeding rotifers containing 2.83mg/g taurine to Pacific whiteleg shrimp *Litopenaeus vannamei* enhanced developmental morphological changes of shrimp larvae as well as improved survival (Jusadi *et al.* 2011).

As we described, taurine has diverse array of biological activity and affect normal growth, development, function, and fillet quality of fish. Therefore, it has been approved to use as supplement of fish feed in 2002 in Japan. Because FDA has also approved to use of synthetic taurine in fish feed in US on March 2017, it is expected that practical use of feed with synthetic taurine will be tested for various fish species at large scale production level.

Considering basic science, fish species can be a good model organism to study function of taurine because of its abundance and diverse metabolic ability. Therefore, detailed study on taurine synthetic ability and its control mechanism will lead future achievement such as development of high taurine strain of food fish by breeding program or genome editing technique, etc.

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