UNIVERSIDADE FEDERAL DO RIO GRANDE DO SUL

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CURSO DE ZOOTECNIA

PEDRO HENRIQUE SESSEGOLO FERZOLA

DETERMINATION OF TAURINE PATHWAY AND ITS PHYSIOLOGICAL IMPORTANCE FOR DOGS AND CATS

Porto Alegre

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Trabalho de conclusão de curso apresentado como requisito para obtenção do grau de Zootecnista, Faculdade de Agronomia, Universidade Federal do Rio Grande do Sul.

Orientador: Prof. Dr. Luciano Trevizan

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Porto Alegre

2019

“All societies have 3 pillars: Wisdom, Strength and Beauty. Treat your body as a beauty temple, your willpower with all your strength and your brain with patience, hard work and wisdom. After that, become the leader who everyone is looking for.”

(Unknown author)

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ABSTRACT

Taurine (2-aminoethanesulfonic) is a unique beta-amino-sulfonic acid that has been discovered by Tiedemann and Gmelin (1827) after isolating taurine from ox bile (WRIGHT, TALLAN and LIN, 1986). The nutritional importance of taurine was first observed by HAYES, CAREY and SCHMIDT (1975). They observed that after three months using casein as a protein source in a cat diet, the cats developed retinal degeneration. The disease was associated to low serum levels of sulfur amino acids due their low concentration in casein. Assuming that the physiological effect was a response to the low levels of taurine in the metabolism, it was possible to determine that taurine is an essential amino acid. Since that, the importance of taurine to metabolic routes have been studied, which was essential to determine that cats can convert just small amounts of taurine due their low activity of cysteine dioxygenase and cysteine sulfinic acid decarboxylase – two essential enzymes for taurine synthesis. On the other hand, dogs do not require dietary sources of taurine as cats do. Dogs can synthesize taurine from methionine through the transmethylation and transsulfuration pathway. Also, cats can only conjugate bile salts with taurine, while other mammals also use glycine. During the bile salts syntheses, taurine is conjugated with chenodeoxycholic acid and cholic acid forming the primary bile salts: taurochenodeoxycholic acid and taurocholic acid. The primary bile acids that do not react in the liver with taurine go to the small intestine and are converted into secondary bile acids. After formed, secondary bile salts can also react with taurine forming tauro-deoxy-cholic acid and taurolitocholic acid. Not only important for bile salts syntheses, taurine has been related to metabolic disorders in cats and dogs. The most common disease caused by taurine depletion is dilated cardio myopathy, which is directly correlated to serum taurine low levels. Despite dogs have the ability to synthesize taurine through sulfur amino acids, the literature has been relating cardio myopathy disease in large breed dogs with low taurine serum levels. This effect in dogs still not completely understood, but has been related to dog's maintenance energy requirement and certain fibers, which can bind with taurocholic acid in the small intestine and make it unavailable for enterohepatic reutilization (KO et al., 2007; CASE et al., 2011). Showing that dog's vegetable-based diets may need a dietary taurine supplementation as well as cat's diets.

RESUMO

Taurina (2-aminoetanossulfonico) é um ácido beta-sulfônico único, o qual foi descoberto por Tiedemann e Gmelin (1827) após isolar a taurina da bile bovina (WRIGHT, TALLAN e LIN, 1986). Sua importância nutricional foi observada pela primeira vez por HAYES, CAREY e SCHMIDT (1975), que observaram que após três meses utilizando caseína como uma fonte proteica, em uma dieta para gatos, que os gatos desenvolveram degeneração de retina. A doença foi associada com os baixos níveis séricos de aminoácidos sulfurados devido a sua baixa concentração na caseína. Assumindo que o efeito fisiológico foi uma resposta aos baixos níveis de taurina no metabolismo, foi possível determinar que taurina é um aminoácido essencial. Com isso, diversos estudos tem sido realizados para avaliar a importância da taurina e sua rota metabólica, o que possibilitaram determinar que gatos conseguem converter apenas pequenas quantidades de taurina devido a sua baixa atividade de cisteína dioxigenase e cisteína ácido sulfínico descarboxilase – duas enzimas essenciais para a síntese de taurina. Por outro lado, cães não exigem fontes dietéticas de taurina como os gatos. Cães podem sintetizar taurina a partir de metionina através da rota da transmetilação e transulfuração. Além disso, gatos conseguem conjugar sais biliares somente com taurina, enquanto outros mamíferos também utilizam glicina. Durante a síntese de sais biliares, a taurina é conjugada com o ácido quenodesoxicólico e ácido cólico formando os sais biliares primários: ácido tauroursodesoxicólico e ácido taurocólico. Os ácidos biliares primários que não reagem no fígado com taurina vão para o intestino delgado e são convertidos em ácidos biliares secundários. Após formados, sais biliares secundários podem reagir com taurina formando o ácido taurodesoxicólico e o ácido taurolitocólico. Importante não apenas para a síntese de sais biliares, a taurina tem sido relacionada com desordens metabólicas em cães e gatos. A doença mais comum causada pela depleção de taurina é a cardiomiopatia dilatada, o qual está diretamente com baixos níveis de taurina sérica. Apesar de cães terem a habilidade de sintetizar taurina a partir de aminoácidos sulfurados, a literatura tem relacionado a doença de cardiomiopatia em cães de raças grandes com baixos níveis séricos de taurina, o qual se liga com o ácido taurocólico no intestino delgado e se torna indisponível para a reutilização enterohepática (KO et al., 2007; CASE et al., 2011). Mostrando que dietas para cães a base de vegetais podem necessitar de suplementação de taurina assim como as dietas para gatos.

SUMMARY

1. INTRODUCTION

Sulfonic acids are members of the organosulfur compounds class with the general formula R-S(=O)$_2$-OH. The radical R can be and organic alkyl or an aryl group and the S(=O)$_2$-OH group a sulfonyl hydroxide. The sulfonic acid group S(=O)$_2$-OH features a tetrahedral sulfur center, which means that the sulfur is at the center of three oxygen atoms and the radical. The most common radicals are aromatic chains known for their artificial sweetener usage.

In some cases, the sulfonic acid group reacts with an amine group, which naturally forms taurine (2-aminoethanesulfonic). Taurine is a unique beta-amino-sulfonic acid (Figure 1) that has a highlighted physiological importance to the animals, especially for cats due to their highly requirement. Taurine's metabolic route is a sulfur amino acids pathway dependent. It depends on methionine which is synthesized to cysteine through the transmethylation and transsulfuration metabolic pathway.

Taurine was discovered by Tiedemann and Gmelin (1827) from ox "Bos Taurus" bile isolation (WRIGHT; TALLAN; and LIN, 1986; WRIGHT and GAULL, 1988; GAULL, 1989). Since then, many researches have been done to determine taurine and taurine derivates importance in the metabolism. Until the 1970's, taurine was thought to be only a biochemically inert end product of methionine and cysteine metabolism, along with inorganic sulfate (WRIGHT and TALLAN et al, 1986).

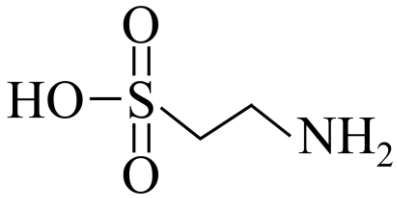
The determination of taurine as an essential amino acid for cats was done by HAYES, CAREY, and SCHMIDT (1975). They have observed that cats fed casein diets had retinal degeneration within three months. The retina is known to have a high level of sulfur containing amino acid (especially taurine) in mammalians. As casein has low levels of sulfur amino acids, it was related to be the cause of retinal degeneration.

For that, they have fed eleven kittens and seven adult cats with semi purified diets containing casein for periods of 12 to 52 days. Taurine plasma and retinal concentration decreased 80% after 24 weeks fed casein diet, and also, decreased 13% retinal DNA expression, which is correlated to the degeneration. Based on these findings, researchers have concluded that retinal degeneration is related to sulfur amino acids levels.

Notwithstanding the foregoing, taurine acts directly as a neurotransmitter or indirectly as a regulator of calcium flux influencing membrane potential and the excitability of nerves and muscles (HAYES, CAREY and SCHMIDT, 1975). Based on that, researchers have observed

that cats have a disadvantage when compared to rats and dogs. Cats do not have the ability to decarboxylate cysteine sulfinic acid to taurine as well as other mammalians. So, cat requires higher levels of amino acids for their maximum growth and maintenance.

Figure 1 - Taurine molecule structure



Pion et al. (1987) have also observed the importance of taurine for companion animal nutrition. They have correlated taurine levels to dilated cardio myopathy (DCM) in twenty-three cats diagnosed by echocardiography at the University of California Veterinary Medical Teaching Hospital. Cats were fed depleted taurine diets for four years to observe the effects of taurine in the heart. At the end of the study, they have shown that chronic taurine depletion causes DCM and have suggested that it could be observed in other species.

Despite taurine is not present into large proteins - as most of the amino acids - it is indispensable for animal tissues. Most mammals need taurine and glycine to conjugate primary and secondary bile salts. Also, most mammals can use only glycine to conjugate bile salts when taurine is in low serum levels, signaling hepatobiliary and ileal disorders (GARBUTT et al., 1969). However, cats lack the ability to conjugate bile salts with glycine, therefore, they conjugate bile salts almost exclusively with taurine (HICKMAN et al., 1991).

As taurine is found in animal tissues – but not in plants – it is necessary to use animal protein sources or synthetic taurine in diets for cats. Its addition in cat diets has been essential to avoid retinal and cardio diseases. Also, with the recent cardio myopathy founds related to taurine deficiency in large breed dogs it becomes important to analyze the effects of vegetarian and vegan diets (without synthetic taurine addition) in dog metabolism.

2. TAURINE SYNTHESIS

2.1. Methionine

Methionine is a sulfur amino acid essential for proteins biosynthesis in dogs and cats. It is a dietary indispensable amino acid because it cannot be synthesized in sufficient amounts to sustain normal growth in mammals (SHOVELLER et al., 2005). Methionine and cysteine

requirements are directly related because cysteine can be synthesized from methionine via enzymatic processes. Due to that, methionine and cysteine requirement is considered together to feed formulation as sulfur amino acid (SAA).

Methionine can be obtained by animal meat and vegetables as well – although vegetable protein quality tended to be lower when compared to animal sources once essential amino acids tend to be diluted with non-essential ones (SAKOMURA et al., 2014). Despite animal protein sources can have high levels of essential amino acids, its incorporation in the diets increases the price of commercial diets. So, commercial sources (DL-methionine and L-methionine) are commonly added to vegetable sources of protein to reduce cost of formulations (NRC, 2006).

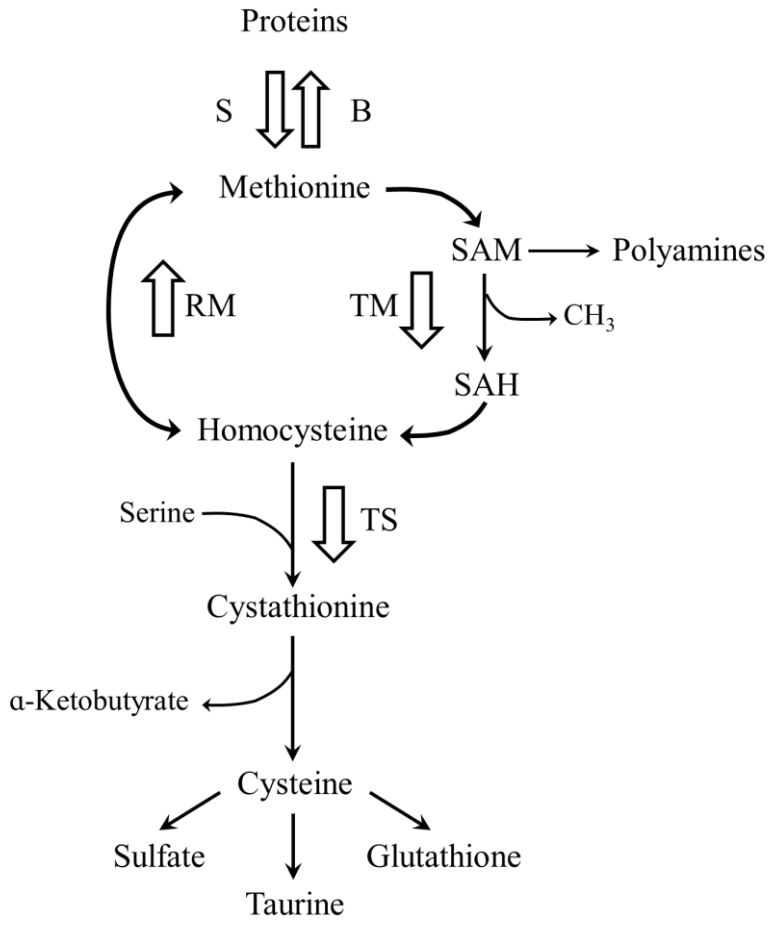
According to SHOVELLER et al. (2005) about 50% of the methionine in the diet is converted to cysteine, and its addition as dietary commercial source, could reduce methionine requirement as much as 80%. Besides that, methionine has three important metabolic functions: transmethylation, to form a primary methyl donor; transsulfuration, to form cysteine; and protein synthesis (Figure 2).

Dogs and cats do not have the same sulfur amino acid requirement. Comparing kittens and puppies, it is possible to observe that growing cats have a requirement 25% higher than growing dogs. Puppies have a minimum requirement of 1.40 g / 1000 kcal of metabolizable energy. While kittens in the same physiological age need 1.75 g / 1000 kcal of metabolizable energy (NRC, 2006; CASE, et al., 2011).

MACDONALD et al. (1984) suggested that cats have a higher requirement due to its hair (that is thicker than other mammals) and for the need to synthesize a unique SAA called felinine. Which is a branched-chain, sulfur-containing α-amino acid (2-amino-7-hydroxy-5,5-dimathyl-4-thiaheptanoic acid) synthesized in the liver and found in the urine of cats Despite its biological function has not been well understood it is suggested that felinine is involved in lipid metabolism and is a pheromone, for territorial marking (NRC, 2006).

The first step to synthesize cysteine is the transmethylation of methionine to form homocysteine. This reaction be done in two pathways: 1) Homocysteine can be formed straight from methionine by the removal of its terminal methyl group. 2) Methionine is converted into S-adenosylmethionine (SAM), which will act as a cofactor that is used as a methyl donor. This reaction is done to form polyamine, but during it a methyl group is released and converted in S-adenosylhomocysteine (SAH) (SHOVELLER et al., 2005).

Figure 2 - Methionine pathway illustrating its metabolic functions, transmethylation (TM), transsulfuration (TS), remethylation (RM), protein synthesis (S), breakdown (B), S-adenosylmethionine (SAM), and S-adenosylhomocysteine (SAH)



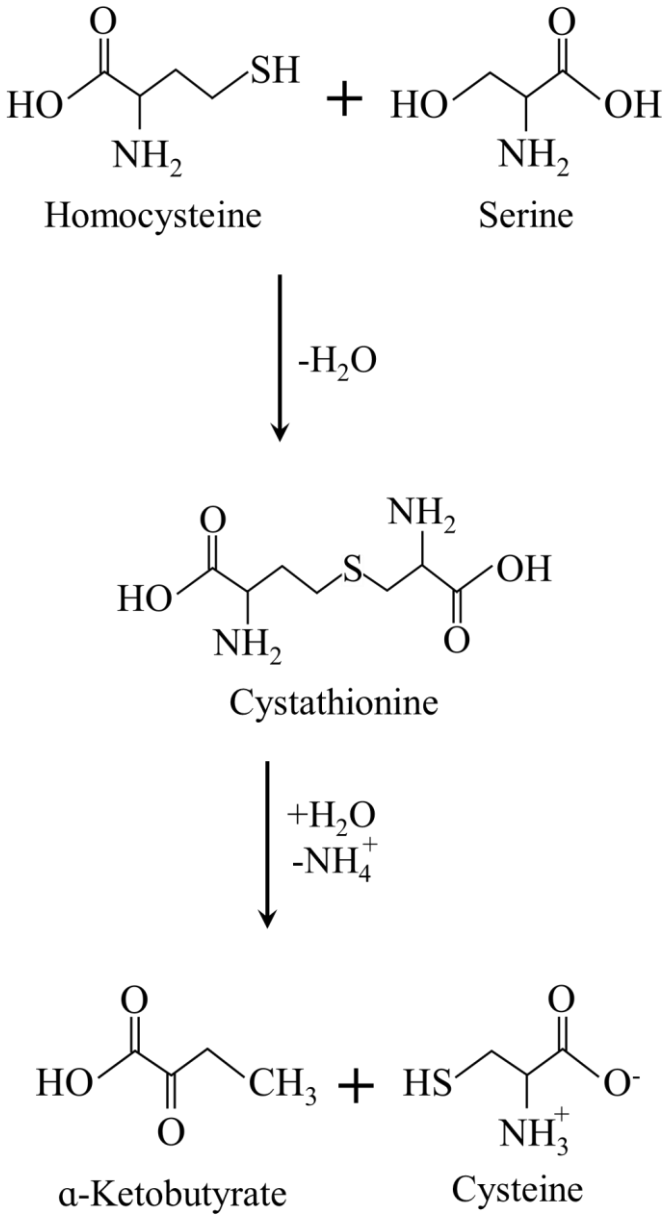
Source: Adapted from SHOVELLER et al., 2005

S-adenosylhomocysteine is a substrate produced by SAM cycle. Once produced, SAH is hydrolyzed to form adenosine or homocysteine by *S*-adenosylhomocysteine hydrolase. Homocysteine is a non-protein α-amino acid that is known as a homologue of cysteine, which is differed from cysteine by the additional methylene group before the thiol group.

Homocysteine can be remethylated to methionine by transferring a methyl group by cobalamin-dependent or cobalamin-independent route. After remethylated, methionine can be converted again in SAM or be used in other metabolic functions. Also, homocysteine can go to the transsulfuration pathway to produce cysteine, where homocysteine reacts with a serine to form cystathionine – an intermediate in the cysteine synthesis. This reaction is catalyzed by the cystathionine beta synthase enzyme and the pyridoxine cofactor (SHOVELLER et al., 2005).

Cystathionine can react with the enzymes: cystathionine gamma-lyase, cysteine dioxygenase, and sulfinoalanine decarboxylase. The metabolic interaction with these enzymes is done to form cysteine and α-ketobutyrate (Figure 3). Also, cystathionine can go to another metabolic route and react with the enzymes glutamate–cysteine ligase and glutathione synthetase to produce glutathione, a water-soluble antioxidant.

Figure 3 - Homocysteine transsulfuration pathway forming cystathionine and cysteine plus α-ketobutyrate formation

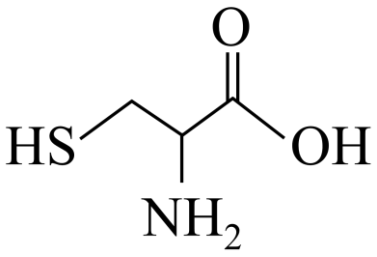


Source: Elaborated by the author, 2019

2.2. Cysteine

Cysteine is a non-essential sulfur-containing amino acid (Figure 4) and methionine dependent in mammalians. It is important for protein synthesis, detoxification and many metabolic functions. Cysteine has a special polarity for its sulfhydryl group (thiol), which can make weak binds with hydrogen, oxygen or nitrogen. Cysteine is oxidized to form cystine, a covalent dimeric amino acid, where two cysteine molecules are linked by a disulfide bind to form the cystine. The disulfide link is important in several proteins due its covalent connections between polypeptides or different polypeptide molecule chains (NELSON and COX, 2014).

Figure 4 - Cysteine molecule structure



Increased levels of cysteine have been related to Parkinson's and Alzheimer's diseases. Also, cysteine produces sulfate and its irregular ratio have been observed in patients diagnosed with Lupus Erythematosus and rheumatoid arthritis. Also, cysteine dioxygenase (CD) ezyme activity, when declined, has been associated to iron accumulation in the body, which might lead to neurological disorders, such as Hallervorden-Spatz syndrome (MCCOY et al., 2008).

Cysteine body concentration is regulated by CD which has a high response to protein and sulfur amino acid consumption. Its activity increases when there is an abundant amount of cysteine supply, avoiding the cytotoxicity. And when the cysteine is scarce, the enzyme activity is reduced to conserve cysteine (STIPANUK et al., 2008; JERKINS and STEELE, 2019).

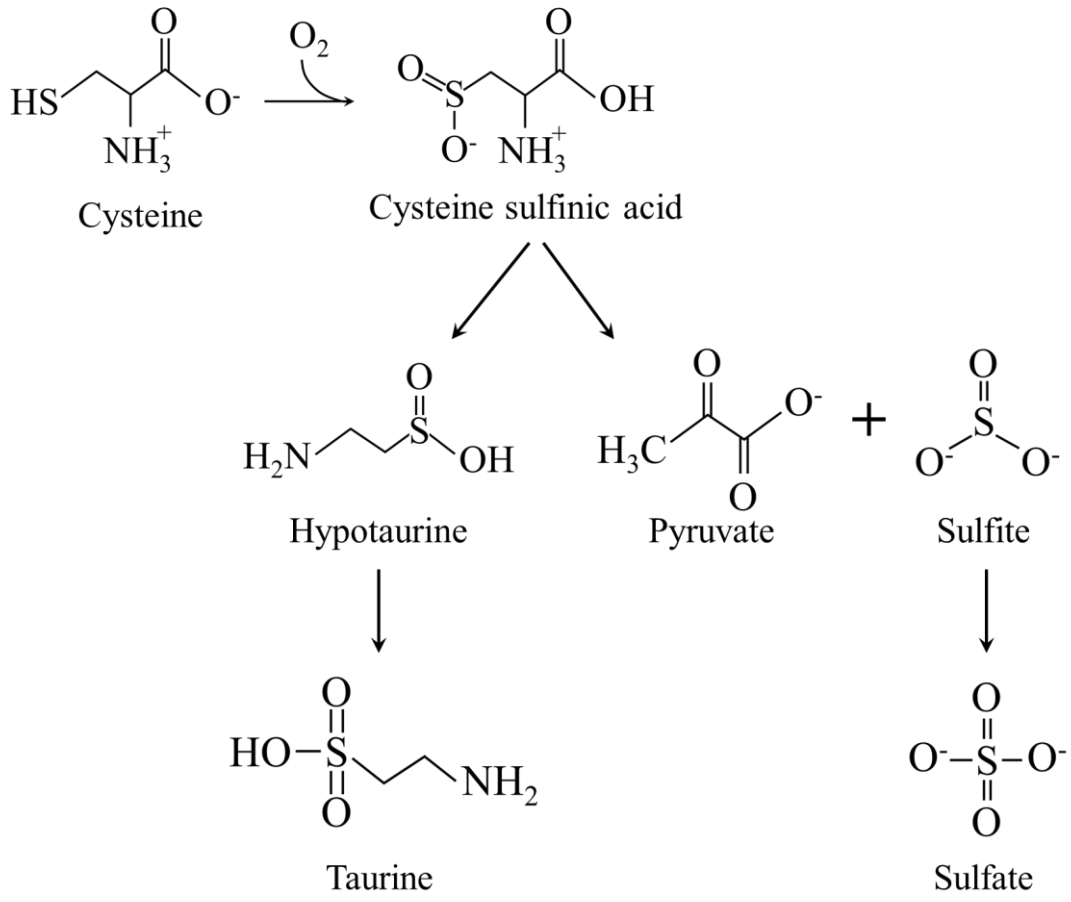
Cysteine dioxygenase can be found in many different tissues, but its activity is higher in the liver and adipose tissues. When cysteine is available in the body, CD catalyzes it by adding two oxygen atoms in its molecule structure and converts cysteine to cysteine sulfinic acid (CSA), which has two different pathways: CSA decarboxylation and CSA transamination (alternative route) leading to different products (Figure 5).

CSA decarboxylation: This route involves the metabolic sequence cysteine, CSA, hypotaurine and taurine (biochemistry of sulfur). In this pathway CSA is oxidized to cysteic

acid, and can be decarboxylated to hypotaurine which is oxidized to form taurine. Also, cysteic acid can be transaminated to β-sulfinyl pyruvate. These reactions happen in the liver and are converted according to the substrate concentration.

CSA transamination: In this pathway, CSA is transaminated to the putative intermediate 3-sulfinylpyruvate after react with α-ketoglutarate forming a glutamate. At the end, this reaction forms pyruvate and sulfite. After that, sulfite is oxidized to sulfate by sulfinic oxidase.

Figure 5 - Cysteine pathway: cysteine sulfinic acid resulting in two produtcs. First, hypotaurine which is converted in taurine. Second, pyruvate and sulfite, being sulfite converted in sulfate



Source: Adapted from DOMINY et al., 2006

Using these pathways, CD controls the concentration of cysteine in the metabolism, increasing or decreasing the catalyzes. Also, these reactions are necessary to control sulfite/sulfate and hypotaurine/taurine production through CSA reactions. In addition, CSA metabolic route has secondary effects that may lead to other synthesis (e.g. sulfoxidation flux).

2.2.1. Cysteine Dioxigenase regulation

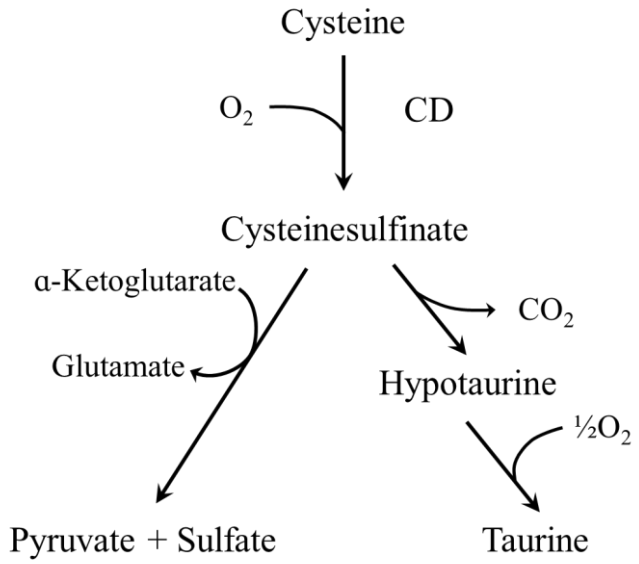
Cysteine dioxigenase regulation in the liver: The accumulation of hypotaurine in tissues and lower conversion into taurine represents a *de novo* synthesis and it is highly correlated with CD flux. As the hepatic CD concentration is strongly related to cysteine availability, changes in methionine ingestion levels may affect its stabilization. Cats and dogs produce proteasome inhibitor 1 to stabilize CD when they are submitted to low protein diets.

The proteasome inhibitor 1 degrades CD and ubiquinates CD intermediates accumulation in the liver. Based on metabolic analyses, STIPANUK et al. (2008) have observed that proteasome inhibitor 1 has a secondary effect in taurine synthesis, it increases hypotaurine accumulation and reduces taurine formation. The authors also observed that when taurine conversion is reduced the excess of hypotaurine, in the liver, is oxidized to sulfonic acids by non-specific oxidizing agents (e.g., hydroxul radicals, singlet oxygen, peroxynitrite).

Cysteine dioxigenase regulation in adipose tissues: The second highest CD concentration site is the adipose tissues, specially the screening tissues. As well as the liver, CD activity in fatty tissues is cysteine dependent. STIPANUK et al. (2008) have analyzed the intake variation effects in rats and concluded that cystine consumption levels affects directly CD activity, which is has a sequential effect in CSA affecting products syntheses (Figure 6).

On the other hand, CD activity in adipose tissues is not methionine dependent. Because there is a lack of an active transsulfuration pathway, S-adenosylhomocysteine and cystathionine – as a substitute for cysteine – cannot prevent CD degradation due to their pathway as well.

Figure 6 - Cysteine pathway: Cysteine dioxygenase (CD) being oxidized in cysteinesulfinate, which leads to taurine synthesis through hypotaurine oxidation. Also, pyruvate and sulfate syntheses after a reaction with α-ketoglutarate



Source: Adapted from STIPANUK et al., 2008

3. BILE ACIDS SYNTHESES

The bile synthesis occurs in the liver and has many components such as bile acids, bilirubin, phospholipids and cholesterol. Bile acids are highlighted for been in-charge of 70% of the reactions in the bile synthesis. These components can react with specific amino acids (glycine and taurine) to form bile salts, which are detergents with higher polarity and effectiveness.

The complete synthesis of bile salts can be divided in three processes. The first step is the hydroxylation, where cholesterol goes to the liver and reacts with two different enzymes to produce the primary bile acids. The second step is the conjugation of the primary bile acids, where these bile acids react with taurine and glycine. Some of these primary bile acids do not react in the liver and go to the intestine, where the secondary bile acids are formed.

3.1. Hydroxylation

Cholesterol comes to the liver via the exogenous pathway of chylomicrons or by the synthesizes of the acetyl CoA excess – also during the recycling lipoprotein pathway. Once cholesterol is in the liver it passes through the smooth endoplasmic reticulum where there are

two reactions that the cholesterol can be involved in. On the first one, cholesterol reacts with the 7 alpha-hydroxylase enzyme (CYP7A1) forming the chenodeoxycholic acid.

On the second one, cholesterol reacts with 12 alpha-hydroxylase enzyme, which forms the cholic acid (Figure 7). The CYP7A1 is the key enzyme in this pathway because it is the rate limiting step, when there is chenodeoxycholic acid and cholic acid in excess in the metabolism. These bile acids can allosteric control and inhibit the CYP7A1 enzyme, which stops the cholesterol conversion into primary bile acids, regulating the metabolic route.

After hydroxylation the primary bile acids can be conjugated with taurine and glycine to form bile salts. Or else, primary bile acids can go to the biliary canaliculi, where they access the biliary system by specific transporters (e.g. Bile Salt Export Pump). On this pathway, the bile acids react in the intestine and form the secondary bile salt, and be reabsorbed in the liver or excreted in through the bile acid pool (Figure 7).

3.2 Conjugation

The conjugation of bile salts are amino acids dependent and is necessary to polarize the molecules to improve their effectiveness. This conjugation happens specifically with glycine and taurine, and the ideal glycine:taurine ratio for most mammals is 3:1 (GARBUTT et al., 1969). In dog's metabolism, glycine and taurine are conjugate with both primary bile acids, which results in four different bile salts: glycochenodeoxycholic acid, taurochenodeoxycholic acid, glycholic acid and taurocholic acid.

However, cats do not have the ability to conjugate bile salts with glycine, conjugating almost exclusively with taurine (HICKMAN et al., 1991; CASE et al., 2011). For that, taurine reacts alone with chenodeoxycholic acid cholic acid forming two bile salts: taurochenodeoxycholic and taurocholic acid. When these primary bile acids do not react with amino acid they go to the intestine, where they can be absorbed or converted into secondary bile acids.

3.2. Secondary bile acids

The common bile duct and the main pancreatic duct combine forming the ampulla of Vatter (hepatopancreatic ampulla) located at the major duodenal papilla. Therefore, primary bile acids can be dehydroxylated by bacterial enzymes (e.g. 7 alpha-dehydroxylase) in the small intestine. Once metabolized, they are converted into secondary bile acids, which can be used to emulsify fat or return to the liver through the entero-hepatic circulation.

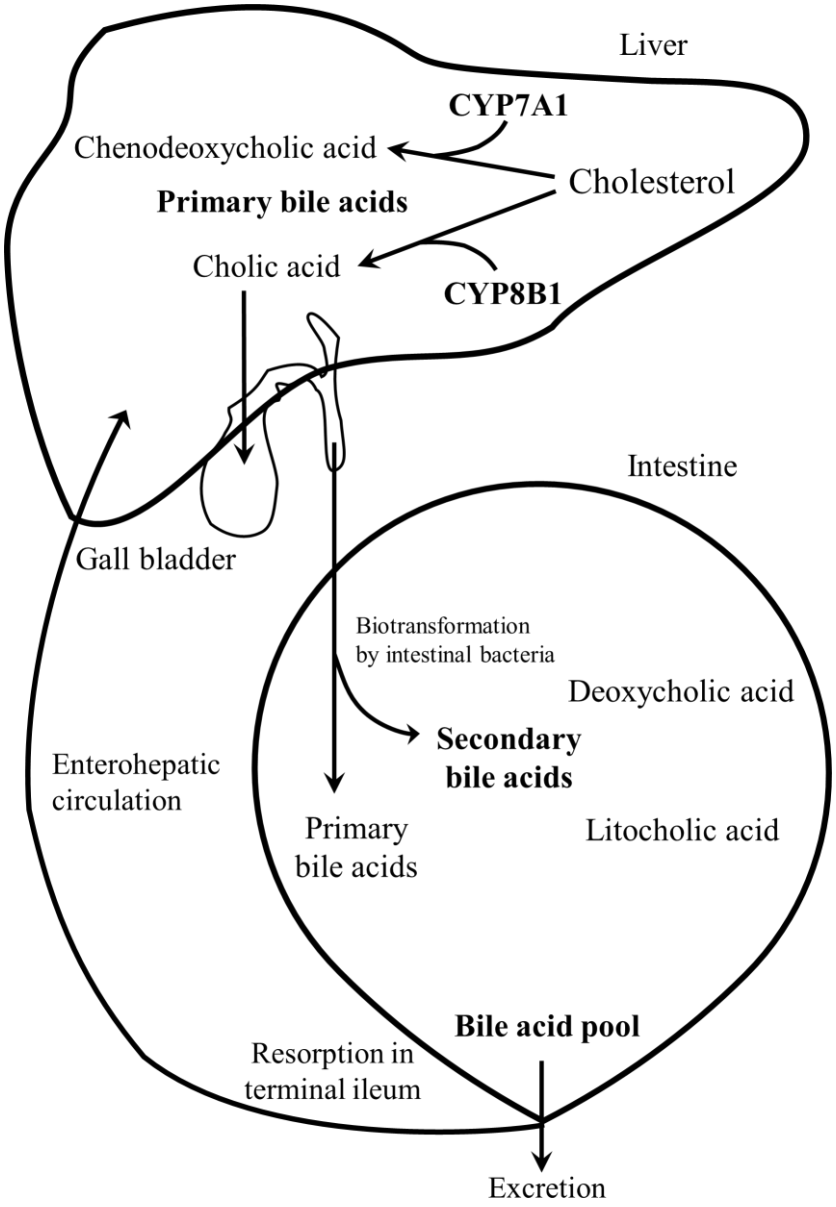
After the dihydroxylation, two new bile salts are formed, the deoxycholic acid and litocholic acid. As well as the primary bile acids, they can be conjugated with glycine or taurine – except cats that use only taurine – to form: glyco-deoxy-cholic acid, tauro-deoxy-cholic acid, glycolitocholic acid and taurolithocholic acid.

The ideal glycine:taurine ratio used in for primary bile acids (3:1) can be used as a standard for the secondary bile acids. Higher ratio levels induced by low taurine ingestion have been analyzed in humans and rats, and they were correlated to ileal disorders or a hepatobiliary issue during the conversion of primary bile salt to secondary (DANIELSSON and SJÖVALL, 1975).

Low levels of secondary bile salt affect the polarization of molecules, the emulsification of fat in the small intestine, and the action of lipase as a secondary effect. Secondary bile acids can result in the formation of micelles, which increase the surface area of lipase and arranges molecules into water-miscible forms that are able to gain access to the aqueous layer covering microvilli, which makes the fat absorption in the body easier.

Moreover, there is a small quantity of these bile acids that are excreted with the primary bile salts in the bile acids pool. But, most of the secondary bile acids are reabsorbed by active and passive transport processes in the jejunum and ileum. Then, they return to the liver via the portal vein to complete the enterohepatic circulation (HICKMAN et al., 1991).

Figure 7 - Cholesterol reactions in the liver forming the primary bile salts, followed by the transition of primary bile acids to the intestine to form secondary bile acids and its resorption



Source: Elaborated by the author, 2019

4. TAURINE REQUIREMENT

4.2. Cats requirement

The importance of taurine for cats has already been explained by its low capacity of synthesizing taurine due to the low activity of CD. Also, for the sulfite and pyruvate rather than taurine by the competing metabolic route. Nonetheless, the early studies of low taurine effects in the metabolism of the cat helped to determine its requirement.

Taurine has an important function on reproductive success in queens. Gestating cats do not have a specific requirement for taurine, it is not necessary for queen's estrus cycle or ability to ovulate. Although, for females, taurine-depleted are more likely to resorb and abort fetuses. Moreover, the low levels of taurine are related to kittens with lower weight at birth and growth rate issues (CASE et al., 2011).

Taurine is affected by heat during feed process due its reaction with gums, then wet cat food contains approximately 2 to 2.5 times more taurine than a dry extruded food (KIM, ROGERS and MORRIS, 1995; FEDIAF 2019). The NRC (2006) recommends that 0.1% of taurine for dried commercial diets, and 0.17% for canned diets. FEDIAF (2019) and AAFCO (2013) recommend 0.1% of taurine for extruded diets as well. Although, for canned diets both suggest 0.2%.

The composition of the diet may affect the bioavailability of dietary taurine. According to KIM et al (1990), heat processing food have a marked effect on the fate of dietary taurine in the cat. They suggested that a greater amount of taurine reaches the lower intestine when heat-processed, and then available for bacteria degradation. Also, certain fibers and peptides can get linked to taurocholic acid in the small intestine, which makes it unavailable for the enterohepatic reutilization (CASE et al., 2011).

4.3. Dogs requirement:

Despite dogs have the capacity to synthesize sufficient taurine from sulfur amino acids, low plasma or low whole-blood taurine levels can be observed in dogs fed low protein diets, or foods with food that are have low Sulphur-containing amino acids (FEDIAF, 2019). Dogs fed some certain lamb and rice foods may have a higher risk of low taurine, because these ingredients have a lower bioavailability and increased fecal losses of taurine, possibly caused by the rice bran (TORRES et al., 2003; FEDIAF, 2019)

It is uncommon to add taurine to commercial diets for dogs. Although, in the last few years several dogs were found with DCM – especially large breed dogs- and the cause related to low levels of taurine plasma. Usually, dogs with DCM are fed low protein diets (10% dry matter basis). According to SANDERSON et al. (2001) healthy adult dogs fed a low protein diet for four years had a significant reduction in plasma taurine concentration, even though the diet met AAFCO guideline recommendations for protein and individual amino acids.

According to the NRC (2006), there are no reports about dose-response of taurine for dogs fed diets that cause taurine deficiency. Dogs can naturally make a large quantity of taurine by dietary sulfur amino acids. Therefore, the adequate addition of sulfur amino acids in the diet is essential to guarantee that there is enough cysteine in the metabolism to supply its requirement. Otherwise, dogs can become deficient in taurine and exhibit clinical signs of dilated cardio myopathy (SANDERSON et al., 2001; NRC, 2006).

Despite the lack of information about taurine requirement, companies that formulate diets with low protein content usually add 1,000 mg of taurine to guarantee the body pool (NRC, 2006). Also, these companies formulate based in the recommendations of different guidelines for sulfur amino acids, aiming to reach an adequate quantity of methionine to be metabolized in cysteine and synthesized in taurine.

The association of American feed control officials suggests 0.70% for puppies and bitches as a minimum requirement of total sulfur amino acids. Also, AAFCO (2013) recommends 0.65% as a minimum for adult maintenance dogs. In addition, the NRC (2006) and the FEDIAF (2019) agree with the AAFCO recommendation for early growth and reproduction. However, while the NRC recommends 0.62% of sulfur amino acids for adult maintenance dogs, FEDIAF has a lower recommendation, which is 0.53%.

5. HEALTH ISSUES

5.1. Dilated Cardio Myopathy

The most common disease related to taurine deficiency is dilated cardio myopathy (DCM), which occurs in the myocardium with impaired systolic pumping function in the ventricles (FASCETTI, A. J. et al., 2003). DCM is the second most observed heart disease in dogs and - despite rare in healthy cats - used to be frequently observed in cats fed unbalanced diets and low levels of serum taurine (CASE et al., 2011).

Even unknowing the exact biochemical effect of taurine in the heart. It has been related to cats with low levels of taurine plasma and myocardial which lead to DCM. Analyzing the effect of taurine in the heart, it seems to have a calcium- and potassium-stabilizing effect on heart tissue and might ensure cationic stability and membrane integrity.

Moreover, dog's size has been related to DCM and taurine requirement. KO et al. (2007) have analyzed the effect of energy requirement in taurine synthesis rate among dogs small and large dogs. The authors have done two experiments, on the first one the dogs were fed enough

diet to maintain their body condition score. And on the second experiment the animals were fed based on the sulfur amino acid requirement per metabolic body weight.

The authors found that even feeding enough food to keep the body score, large dogs had a lower taurine biosynthesis rate and their mean plasma and blood taurine concentration were indicating marginal taurine status. And also, one large dog had plasma taurine concentration similar to the levels reported for dogs with DCM, that was corrected after taurine supplementation.

On the other hand, when the authors fed the animals based on the SAA requirement per metabolic body weigh both sizes had a higher intake. Although, large dogs showed a larger necessity. After the adjustment, small dogs increased their intake in 24 ± 4 % while large-breed dogs were 69 ± 15% higher. These experiments indicate that the difference in taurine biosynthesis is related to SAA intake rather than expected energy needs.

5.2. Feline Central Retinal Degeneration

Feline central retinal degeneration (FCDR) is described as a bilaterally symmetrical lesion of the area centralis (BELHORN, AGUIRRE and BELHORN, 1976). Taurine affects primarily the photoreceptor cells, which regulates the flux of calcium and potassium ions across the photoreceptor pigment-epithelial cell barrier. The photoreceptor cell membrane disrupts when the levels of taurine are low, which leads to a cellular death and the loss of cells.

According to HAYES, CAREY and SCHMIDT (1975) kittens and adult cats fed free-taurine diets developed FCRD within three months. Also, researchers have found that after 23 weeks consuming low levels of taurine the area centralis was affected and structural changes indicated photoreceptor cell degeneration. Even the detection of abnormalities in electroretinograms can be observed with six weeks of depletion. Visual impairment is only observed clinically just after 20 weeks. At this point, blindness usually occurs in the cats (CASE, et al., 2011).

Nonetheless, dogs are also susceptible to retinal degeneration due to plasma taurine deficiency. Pion et al. (1998) have reported that three American Cocker Spaniels with low plasma taurine concentration were observed to have bilaterally symmetrical hyper-reflective retinal lesions similar to those seen in cats with FCRD. This report highlights the importance of taurine to dog's metabolism as well as for cat's, and that taurine depletion may affect the heart function, the retina, or even the reproductive capacity (PION et al, 1998; NRC, 2006).

6. CONCLUSION

The sulfonic acid taurine (2-aminoethanesulfonic) plays an important role in dogs and cats' metabolism. Since taurine was discovered, several trials have been done to analyze its metabolic pathway and essentiality for companion animal. Taurine is usually related to cats, because it is directly related to retinal degeneration and dilated cardio myopathy.

Despite dogs can synthesize taurine through the methionine pathway (transmethylation and transsulfuration), there are several physiological reactions that can affect its formation. Not only methionine-dependent, taurine synthesis is directly related to cysteine for cysteine dioxygenase and cysteine sulfinic acid activities, which form hypotaurine.

Taurine is specially required in the metabolism because it acts directly in the conjugation of primary and secondary bile salts. One of the reasons that taurine is highly evaluated in cats is due their inability of conjugating bile salts with glycine. Even in other mammals, bile acids conjugation with taurine is important for its ratio with glycine, which sings ileal disorders.

There is no minimum recommendation for taurine dog requirement in the nutritional guidelines, therefore, to guarantee taurine synthesis, diets are formulated based in total sulfur amino acids. There is an agreement of 0.70% of total sulfur amino acids for growth and gestating dogs. Although the recommendation for adult maintenance varies from 0.53% to 0.65%.

On the other hand, the recommendation for cats is much more analyzed, the nutritional guidelines suggest the minimum taurine requirement based on the diet processing production. As taurine is affected by heat, it is recommended that canned food may have from 0.17 to 0.2% of taurine inclusion, and extruded diets 0.1%.

Nonetheless, taurine has already been classified as essential amino acid, its importance in dog's metabolism still not completely known. Also, new vegetable-based and vegan diets have been related to metabolic disorders - such as dilated cardio myopathy - due to the low levels of taurine in the ingredients, which leads to a metabolic depletion of taurine.

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