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Review

Antioxidant and toxicological effects elicited by alpha-lipoic acid in aquatic organisms

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ABSTRACT

Lipoic acid (LA) is a disulfide-containing compound derived from octanoic acid that is synthesized in mitochondria. This molecule acts as a co-factor for mitochondrial enzymes that catalyze oxidative decarboxylation reactions. Several antioxidant properties of LA enable it to be considered as an "ideal antioxidant", having diverse benefits that allow it to deal with environmental or biological stress. Some of the effects induced by LA in aquatic organisms render it suitable for use in aquaculture. However, it is necessary to determine the appropriate dose(s) to be used with different species and even organs to maximize the beneficial antioxidant and detoxifying effects and to minimize the pro-oxidant toxic effects. This review analyzes and compiles existing data from aquatic organisms in which both benefits and drawbacks of LA have been described.

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1. Introduction

Alpha-lipoic acid (LA) or 1,2-dithiolane-3-pentanoic acid (CAS number: 1200-22-2), is a disulfide-containing compound derived from octanoic acid that is synthesized in the mitochondria and is found in microorganisms, plants and animals (Reed et al., 1974; Navari-Izzo et al., 2002). LA exists as two enantiomers: R-lipoic acid, which occurs naturally, and S-lipoic acid, which can be produced synthetically. The molecule contains two sulfur atoms (at C_6 and C_8) connected by a disulfide bond (Fig. 1a). Once inside a cell the disulfide bond can be reduced to form dihydrolipoic acid (DHLA) (Fig. 1b) and stored bound to proteins, where the enzyme lipoamidase can cleave the complex and release LA for physiological functions (Yoshikawa et al., 1996). However, until now, it has been unclear if the complex LA-bound protein also possesses a physiological role in the organisms as does LA alone.

The practice of aquaculture is growing worldwide, mostly due to increasing demand for seafood for human use (Molina-Poveda and Morales, 2004). However, under intensive culture conditions, aquatic

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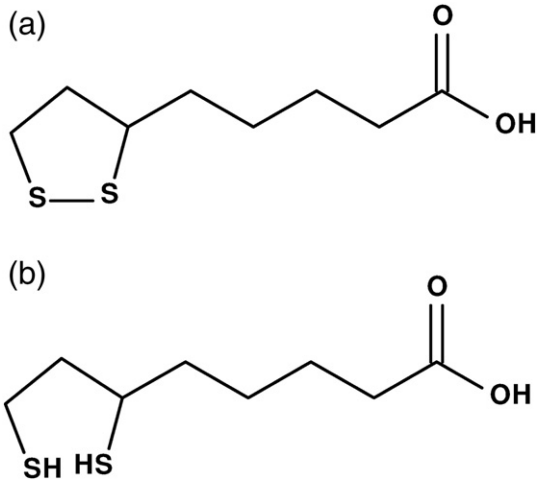

Fig. 1. Molecular structure of the redox pair lipoic acid (LA, a) and dihydrolipoic acid (DHLA, b).

organisms such as fish and crustaceans are subject to factors (both biotic and abiotic) that can affect their production, growth and health as a result of the generation of oxidative stress (Monserrat et al., 2007; Oliva-Teles, 2012). As with all aerobic organisms, cultured aquatic organisms are also susceptible to the damaging effects caused by oxidative stress, and they have substantial internal defenses that are well described in the literature (Ross et al., 2001; Lushchak and Bagnyukova, 2006). Oxidative stress reflects an imbalance between pro-oxidants and antioxidants that favors a disruption in signaling and redox control of cellular and/or molecular damage (Jones, 2006). Reactive oxygen species (ROS) are formed during aerobic metabolism by several biochemical processes and can affect various physiological processes, including the regulation of cellular signaling, gene expression and the antimicrobial defense elicited by the immune system (Butler et al., 2009; Cui et al., 2009). However, high ROS concentrations are harmful to cells, and it has been proposed that this condition triggers the etiology of several pathologies (Lu et al., 2006; Soffler, 2007; Roberts and Sindhu, 2009).

An alternative approach to address the effects induced by oxidative stress is to provide an adequate diet (Gauquelin et al., 2007), accompanied by regular antioxidant supplementation that can improve the response of fish and shrimps to stressful conditions, such as pathogens or insults induced by toxins or pesticides (Wang and Chen, 2005; Puerto et al., 2010; Amado et al., 2011; Monserrat et al., 2013; Saccol et al., 2013). Antioxidant supplementation of aquatic organisms can be considered to be a form of chemoprotection, a strategy for the prevention of diseases through the use of specific diets or by the administration of dietetic supplements (Wolf, 2001). As mentioned above, several factors can trigger oxidative stress, and for this reason, antioxidant supplementation in food can be employed as chemoprotectants. In farm animals, oxidative stress may be involved in several circumstances, including conditions that are relevant for animal production and for the general welfare of the individuals (Lykkesfeldt and Svendsen, 2007). During the rearing process, temporal and spatial alterations in water quality can render the cultured organisms susceptible to oxidative stress. Variations in salinity, oxygen, and temperature and even daily variations of the antioxidant system can alter the ability of the organisms to detoxify ROS (Fanjul-Moles et al., 2003; da Rocha et al., 2009; Maciel et al., 2010). Furthermore, parasite infestation and toxins produced by cyanobacteria, such as microcystin, can also affect the antioxidant capacity of fish (Secombes and Chappell, 1996; Belló et al., 2000; Amado and Monserrat, 2010; Amado et al., 2011; Garcia et al., 2011).

To prevent a pro-oxidant condition, exogenous dietary antioxidants have been employed (Linnane and Eastwood, 2006). The exogenous non-enzymatic antioxidants include ascorbic acid, α-tocopherol, carotenoids and α-lipoic acid (LA). Dietary supplementation with exogenous non-enzymatic antioxidants has been extensively used in humans, pets and farm animals, including aquatic organisms (Block, 1991; Merchie et al., 1996; Moini et al., 2002; Tocher et al., 2002; Rochette et al., 2013).

Based on this view, food supplementation with LA can be expected to improve the antioxidant status of aquatic organisms. The potential benefits afforded by LA in addressing environmental or biological stressors, as well as the improvement of meat quality, will be discussed in the present review. Other biochemical side-effects, including toxic pro-oxidant effects, will also be considered.

2. Uptake and metabolization of lipoic acid

In mammals, according to Bustamante et al. (1998), when LA is offered via dietary supplementation, absorption occurs rapidly in the gut through the monocarboxylate transporter (Shay et al., 2009), although it has been suggested that LA bioavailability is reduced when administered in food because of competition with other nutrients for transporters (Shay et al., 2009). The sodium-dependent multivitamin transporter is also considered to be involved in the gastrointestinal incorporation of LA and in the uptake of this molecule by different tissues as it is transported in plasma (Shay et al., 2009; Rochette et al., 2013). In endothelial cells, May et al. (2006) demonstrated the role of medium fatty acid transporters for LA uptake, as a reduction was verified when octanoate was co-incubated with LA (Fig. 2). However, it is important to note the lack of studies dealing with LA absorption in aquatic organisms.

Once in the cells, LA can undergo β-oxidation (Teichert et al., 2003; Shay et al., 2009) in mitochondria or reductive reactions to produce DHLA, which are important for the recycling of other antioxidants as stated in Section 1. At least three enzymes are known to reduce LA: cytosolic thioredoxin reductase, glutathione reductase and mitochondrial lipoamide dehydrogenase (Pick et al., 1995; Biewenga et al., 1996; Bustamante et al., 1998) (Fig. 2). In the reductive pathways, some important differences exist. As the C_6 is a chiral carbon, LA can occur as an R or S enantiomer. A higher activity of lipoamide dehydrogenase has been verified for the natural R-enantiomer, and a preference for the S-enantiomer has been reported for glutathione reductase (Pick et al., 1995; Biewenga et al., 1996). May et al. (2007) reported a lack of specificity of thioredoxin reductase from human red blood erythrocytes between R and S enantiomers. Additionally, there are currently no studies in aquatic organisms regarding differences in reduction capabilities of LA between organs, an important issue to consider given that LA is typically administered as a racemic mixture. In this context, glutathione reductase activity should be important for reducing the non-natural S enantiomer. The activity of glutathione reductase, in turn, is dependent on NADPH bioavailability, which is linked to the pentose phosphate pathway. Although studies regarding the capacity of pyridine nucleotide disulfide reductases to reduce LA have been performed in human erythrocytes and endothelial cells (May et al., 2006, 2007), such studies are still lacking in cells or tissues from aquatic organisms.

3. Antioxidant and detoxification responses elicited by lipoic acid

3.1. Antioxidant responses

LA is well known as a co-factor of mitochondrial enzymes (pyruvate dehydrogenase and α-ketoglutarate dehydrogenase) that catalyze oxidative decarboxylation (Reed et al., 1974; Packer et al., 1995, 2001), which are crucial for energy metabolism. Furthermore, LA and DHLA have antioxidant proprieties, including free radical quenching and metal chelation (Rochette et al., 2013). LA and DHLA form a redox pair with a reduction potential of -0.32 V, which is low enough for the transfer of electrons and protons to glutathione disulfide (GSSG), ascorbyl