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Free amino acids: an innovative treatment for ocular surface disease

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ABSTRACT

Amino acids are the basic constituents of living organisms, and have both a structural and an active dynamic role in tissue and cell physiology. Human tears contain 23 amino acids, the relative proportion of which may change with the different physiological states of the eye surface. In this review, we present a collection of data from the published literature that indicate an active role of amino acids in the maintenance of eye surface homeostasis. Moreover, another series of published clinical data indicate that supplementation of amino acids, either as food supplements or as a topical treatment in enriched eye drops, is beneficial to the eye surface, and may improve its healing in cases of eye surface disease due to different causes.

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1. Introduction

Dry Eye Disease (DED) was defined in 2007 by the Dry Eye Workshop (DEWS) as 'a multifactorial disease of the tear film and the ocular surface that results in symptoms of discomfort, visual disturbance, and tear film instability with potential damage to the ocular surface'. It is usually accompanied by increased osmolarity of the tear film and inflammation of the ocular surface, and is considered one of the most frequent ocular disorders leading to visual impairment (Foulks, 2007). Current therapeutic approaches are aimed at improving signs and symptoms of DED and are related to its etiology due to either increased tear film evaporation because of a deficiency of the lipid layer, and/or decreased production of the aqueous phase by the main and accessory lacrimal glands.

Currently, therapies can be systemic and/or topical, and they are focused on tear supplementation, retention or stimulation, coupled to the control of the underlying inflammation (Foulks, 2007; Dogru et al., 2013).

Tear supplementation is obtained with topical lubricants, which can be hypotonic or isotonic and differ in their content of electrolytes, surfactants and viscosity agents. Sodium hyaluronate is frequently used as a hydrating and mucomimetic agent since it

increases the stability of the precorneal tear film and improves ocular surface wettability and smoothness thanks to its water retentive and viscoelastic properties (Foulks, 2007; Aragona et al., 2002).

Dry eye treatment by tear stimulation can be achieved by orally administered cholinergic drugs, such as pilocarpine that is used for severe dry eyes in Sjogren's Syndrome. The improvement of ocular surface epithelia results from the stimulation of muscarinic receptors and of the secretory function associated with the increased number of muciparous goblet cells (Foulks, 2007; Aragona et al., 2006).

As regards anti-inflammatory treatment, the efficacy of topical corticosteroids has been reported (Foulks, 2007; Aragona et al., 2013b, 2015). The topical use of cyclosporine was also effective, but its use is still limited to the US and is under continuing investigation (Foulks, 2007; Aragona, 2014; Stonecipher et al., 2013).

Interestingly, oral tetracyclines have demonstrated therapeutic properties in the management of DED. They have been shown to reduce MMP expression, lipase production and collagenase activity, and have been successfully used to treat chronic blepharitis, rosacea and Meibomian Gland Disease (Foulks, 2007; Hessen and Akpek, 2014; Doughty, 2016).

The use of oral supplementation with essential fatty acids was found to be effective as an additional therapy in DED management. Such treatment has been clinically shown to significantly reduce conjunctival inflammatory marker expression (Foulks, 2007; Aragona et al., 2005; Brignole-Baudouin et al., 2011).

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Finally, supplementation with amino acids, topical or systemic, is a relatively recent strategy that will be the subject of this mini review.

2. Amino acids in tears

Amino acids are essential nutrients as they constitute the main elements of which proteins and peptides are made, and thus play an essential part in the regulation of the whole metabolism of living organisms. Amino acids are naturally present in human tears. Their nature has been investigated in two different studies, both of which reported that their relative concentration differs from what is found in serum (ChenZhuo et al., 2002; Nakatsukasa et al., 2011) and that this concentration changes in patients

affected by ocular dryness (Nakatsukasa et al., 2011) (Fig. 1). The presence of free amino acids in tears and their dynamic fluctuations suggest that they may play some relevant physiological role in this specific and special environment. For instance, amino acids may have antioxidant properties: methionine and cysteine work as antioxidants through reversible protein oxidation (Kantorow et al., 2004; Njie-Mbye et al., 2013). In the musculoskeletal system, amino acids are required to increase bone and muscle mass, and to reinforce tendons and joints (Gibala, 2000). In the epidermis, amino acids (more specifically glycine, proline and hydroxyproline) are required for the synthesis of tropocollagen by stromal fibroblasts, and for the building of collagen fibers (Wu et al., 2011). A healthy stroma is also the key to a healthy epithelium, and efficient wound healing depends on a proper cross-talk between fibroblasts and epithelial cells, which can be implemented by the

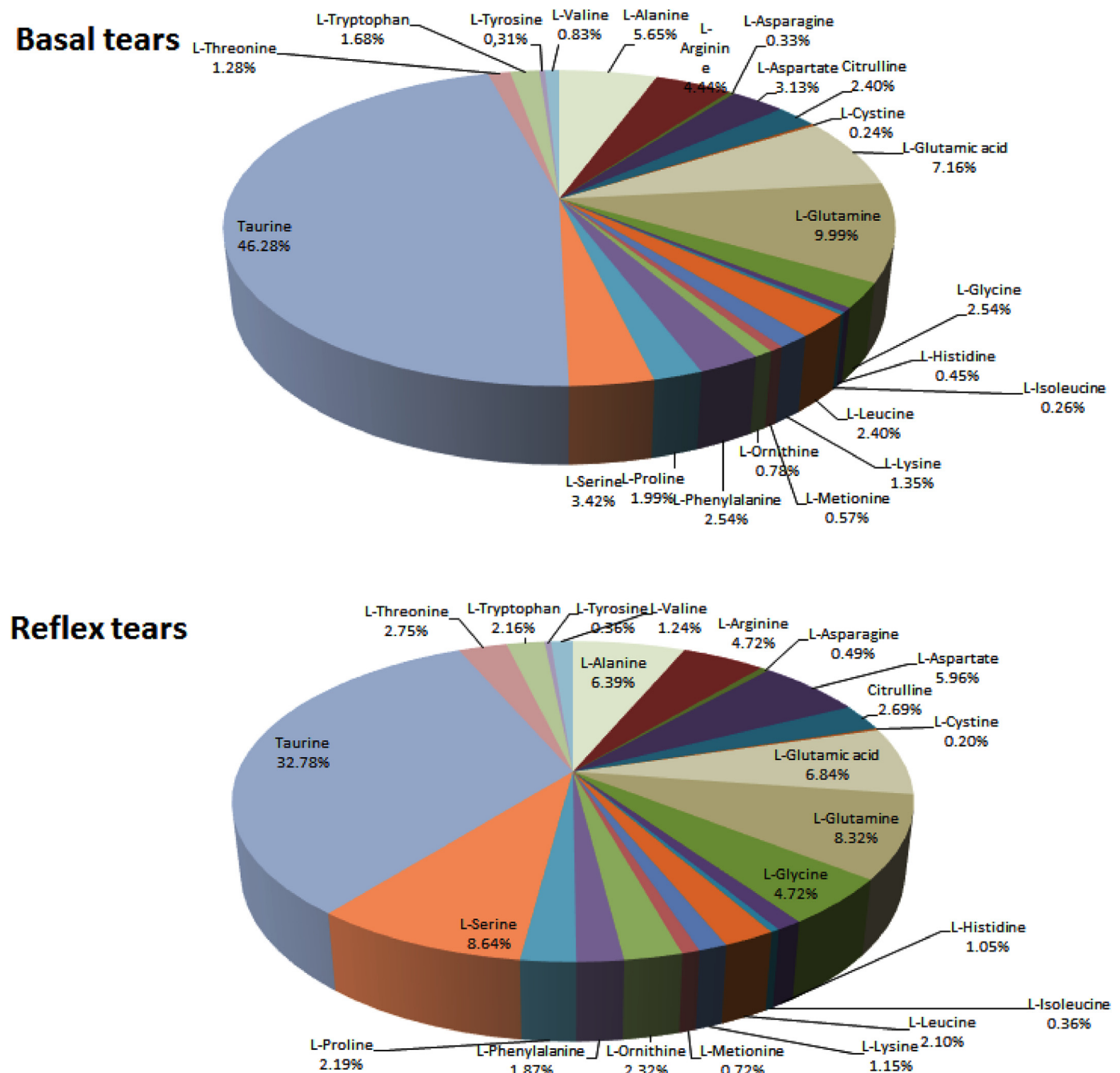


Fig. 1. Concentration of each amino acid in basal and reflex tears (Nakatsukasa et al., 2011).

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