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Major review

Is the main lacrimal gland indispensable? Contributions of the corneal and conjunctival epithelia

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ABSTRACT

The ocular surface system is responsible for ensuring that the precorneal tear film is sufficient in both quality and quantity to preserve optimal vision. Tear secretion is a complex, multifactorial process, and dysfunction of any component of the ocular surface system can result in tear film instability and hyperosmolarity with resultant dry eye disease. The tear film is primarily composed of lipids, aqueous, and mucins, with aqueous accounting for most of its thickness. The aqueous is produced by the main lacrimal gland, accessory lacrimal glands, and corneal and conjunctival epithelia. Although the main lacrimal gland has long been considered an indispensable source of the aqueous component of tears, there is evidence that adequate tear secretion can exist in the absence of the main lacrimal gland. We review and discuss the basics of tear secretion, the tear secretory capacity of the ocular surface, and emerging treatments for dry eye disease.

1. Introduction

The ocular surface system comprises the elements that form, maintain, and protect the ocular surface.[37] The ocular surface system is responsible for ensuring that the tears form a smooth refractive tear film over the surface of the cornea that enables optimal vision. The tears are composed primarily of lipid, aqueous, and mucin, each formed by specialized structures of the ocular surface. The aqueous component of tears is produced by the main lacrimal gland, accessory lacrimal glands, and corneal and conjunctival epithelia. The main lacrimal gland is generally thought to be an indispensable source of the aqueous component of tears; however, there is evidence that adequate tear secretion can exist in the absence of the main lacrimal gland.

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The pathogenesis of dry eye disease is thought to involve tear film instability and hyperosmolarity with resultant mechanical, osmotic, and immuno-inflammatory damage to the ocular surface.[112] It has been estimated that 3.23 million women and 1.68 million men of age 50 years and older in the USA have moderate-to-severe dry eye disease, and the prevalence of dry eye disease increases with age.[103,104] Dry eye disease can negatively affect vision-related quality of life by impairing the performance of activities of daily living such as reading, using a computer, and driving.[80] Severe dry eye has been shown to decrease patient-reported utility values to levels comparable to dialysis and severe angina.[11,106] Harnessing the reserve tear secretory capacity of the ocular surface is an attractive treatment strategy for disorders of the tears and ocular surface, such as dry eye disease. Herein, we endeavor to answer the question: Is the main lacrimal gland indispensable?

2. Current understanding of the basics of tear secretion

2.1. *The ocular surface system*

The interface between the air and the tear film-corneal epithelium complex accounts for approximately two-thirds of the optical power of the eye. Accordingly, a smooth refractive tear film is essential for optimal vision.[93] This requires the coactions of a variety of structures at the ocular surface that are collectively referred to as the ocular surface system.[37] The ocular surface system comprises the tear film, cornea, conjunctiva, meibomian glands, lacrimal glands, nasolacrimal duct, eyelid, and eyelashes, and their interconnected nervous, endocrine, vascular, and immune systems. This interconnectedness allows for communication and collaboration between the various components of the ocular surface system. The lacrimal functional unit,[111] an important subset of the ocular surface system, consists of the cornea, conjunctiva, meibomian glands, lacrimal glands, eyelid, and their interconnected nervous system. The lacrimal functional unit highlights the main structures responsible for tear secretion and the blink reflex. Dysfunction of any component of the ocular surface system can result in abnormalities of the tear film and loss of the smooth refractive tear film.

2.2. *Tear secretion*

Tear secretion is a complex, multifactorial process that involves the nervous, muscular, endocrine, vascular, and immune systems. Tear secretion is a reflex response initiated by stimulation of the ocular surface or nasal mucosa.[38,54] The polymodal nociceptors of the cornea are the primary sensory fibers responsible for initiating tear secretion (Fig. 1).[6] These sensory fibers relay signals to the spinal trigeminal nucleus where information is processed and relayed to the superior salivary nucleus of the pontine tegmentum.[42,79] Preganglionic parasympathetic neurons originating from the superior salivary nucleus project to the pterygopalatine ganglion.[44,124] Postganglionic parasympathetic neurons originating from the pterygopalatine ganglion project to the lacrimal glands, and also presumably to the goblet cells and meibomian glands, where they release neurotransmitters such as acetylcholine and vasoactive intestinal peptide that stimulate tear secretion.[25,77,102] The concepts of basal and reflex tear secretion are frequently used in clinical practice; however, basal tear secretion in the absence of stimuli probably does not occur to a significant extent as evidenced by decreased tear secretion during sleep and under local and general anesthesia.[126] The blink reflex, also known as the trigeminofacial reflex, is critical for tear secretion and function. Blinking stimulates the release of lipids from the meibomian glands and replenishes the tear film with tears from the inferior tear meniscus.[68,94]

2.3. *Tear components*

The precorneal tear film is a gel that coats the glycocalyx of the superficial corneal epithelial cells. Historically, the tear film was thought to be formed by 3 distinct layers: the outer lipid layer, the middle aqueous layer, and the inner mucin layer. Recent findings suggest, however, that there may not be a clear delineation between the middle aqueous and inner mucin layers, given the hydrophilic nature of mucins.[110] The lipids of the outer lipid layer are produced primarily by the meibomian glands, and to a lesser extent by the glands of Zeis. These lipids form a hydrophobic barrier that retards tear evaporation and prevents tear overflow. The aqueous is produced by the main and accessory lacrimal glands, and the corneal and conjunctival epithelia. The aqueous has a variety of essential functions, including facilitating oxygen and nutrient transmission and electrolyte regulation. The mucins are produced primarily by the goblet cells and to a lesser extent by the corneal and conjunctival epithelia and the lacrimal glands of Henle and Manz. These hydrophilic mucins function to stabilize the tear film and ensure that the tear film is evenly distributed.

2.4. *The aqueous*

The aqueous is secreted as a mixture of water, electrolytes, solutes, and proteins. The aqueous accounts for most of the thickness of the tear film. The importance of the main and accessory lacrimal glands in tear production has long been recognized. It was once thought that the main lacrimal gland was responsible for reflex tear secretion, whereas the accessory lacrimal glands were responsible for basal tear secretion; however, based on similarities in innervation, it is now thought that the main and accessory lacrimal glands contribute in unison to both basal and reflex tear secretion.[10] In humans, the main lacrimal gland is an almond-shaped tubuloacinar exocrine gland that lies within the lacrimal fossa of the bony orbit.[24] The primary secretory cells of the main lacrimal gland are the pyramidal acinar cells that line its tubules. The accessory lacrimal glands of Wolfring and Krause are located in the palpebral conjunctiva. The accessory lacrimal glands are thought to be similar to the main lacrimal gland in both form and function. The importance of the corneal and conjunctival epithelia in aqueous production is