Editorial

Ophthalmic Research

Ophthalmic Res 2008;40:2–4
DOI: 10.1159/000111695

Published online: November 28, 2007

New Techniques in Lacrimal Gland Research: The Magic Juice and How to Drill for It

Erich Knop[a] Nadja Knop[b]

[a]Research Laboratory of the Eye Clinic CVK, Charité – Universitätsmedizin Berlin, Berlin, and
[b]Department of Cell Biology in Anatomy, Hannover Medical School, Hannover, Germany

The Lacrimal Gland – the Extended Ocular Surface

Although the lacrimal gland resides in a slightly hidden anatomical location, more or less deeply inside the orbita, it is in fact of the utmost importance for the maintenance of an intact ocular surface and in particular for the preservation of corneal clarity and hence visual function. The majority of the factors that keep the ocular surface healthy and happy are secreted by the lacrimal gland. All together they form the tear fluid which is transported onto the cornea and conjunctiva by downstream flow through the excretory canaliculi [1]. However, research on the gland was somewhat hampered by technical problems in monitoring lacrimal gland function. This appears solved now, at least to a large extent, as reported in a paper by Ding et al. [2] in this issue of *Ophthalmic Research*.

Even though, at first glance, the lacrimal gland appears to reside in a remote location, it forms, along with the lacrimal drainage system, the so-called ocular mucosal adnexa which is connected to the ocular surface proper (cornea and conjunctiva). The ocular mucosal adnexa upstream and downstream of the conjunctiva forms, together with it, a continuous mucous membrane and hence unites the source, the assumed main target and the eventual drainage of the tear fluid. Therefore, in a wider functional sense and also from an embryological view, the lacrimal gland is certainly a part of the ocular surface as an epithelial sprout from the conjunctiva [3]. Unluckily, this fact is often appreciated only if the lacrimal gland and the cornea show pathological alterations.

Functional Interrelations at the Ocular Surface

Functional interrelations of the lacrimal gland and the ocular surface proper have increasingly become the focus of interest in recent years and have helped to deepen our understanding of how the normal state is maintained and how different forms of ocular surface disease can arise. The neural regulation of lacrimal gland secretion that integrates afferent sensory and efferent secretory-motor pathways is described by the 'lacrimofunctional unit' [4]. This concept explains that only sensory stimulation from an intact ocular surface can drive the necessary tear flow required for the wetting and for the trophic survival of the ocular surface tissues. It allows to explain symptoms and disease mechanisms found in the dry eye syndrome and has also pointed to potential therapeutic targets [5]. In terms of immune regulation, it has been shown that the lacrimal gland together with the conjunctiva and lacrimal drainage system forms a continuous 'eye-associated lymphoid tissue (EALT)' [6, 7] that represents the part of the mucosal surface immune system of the body located at the ocular surface and adnexa according to the

KARGER

Fax +41 61 306 12 34
E-Mail karger@karger.ch
www.karger.com

0030–3747/08/0401–0002$24.50/0

Accessible online at:
www.karger.com/ore

PD Dr. Erich Knop
Research Laboratory of the Eye Clinic CVK, Charité – Universitätsmedizin Berlin
Ziegelstrasse 5–9
DE–10117 Berlin (Germany)
Tel. +49 30 450 554 037, Fax +49 30 450 554 903, E-Mail erich.knop@charite.de

standardized nomenclature; it certainly includes the established conjunctival CALT. EALT has all the afferent and efferent components of an integrated immunological feedback loop of the immune answer; it can promote the recirculation of immune cells via specialized vessels and is a prerequisite for the population of the lacrimal gland (and downstream mucosa) with plasma cells that produce antibodies against ocular-surface-relevant antigens [3]. The concept of EALT also explains that the normal ocular surface mucosa including the conjunctiva has a resident population of lymphoid cells that constantly contribute to the maintenance of immune homeostasis and tissue integrity and that do not only immigrate under inflammatory conditions as believed previously. Immunology and lubrication of the ocular surface are interestingly linked and recent years have shown that immune-mediated inflammation is an important primary or secondary mediator of dry eye disease both at the conjunctival level and inside the lacrimal gland [6, 8–10]. (Auto-)immunological processes inside the lacrimal gland itself are an important reason for Sjögren's syndrome, a severe form of dry eye disease, and the analysis why and how the mechanisms of immunological self-tolerance are corrupted inside the gland may provide general insight into mechanisms of the development of inflammatory disease also in the conjunctiva and cornea [10–12].

Tear Composition and Function Are Key Elements of Ocular Surface Integrity

The 'magic juice' that keeps all the business going at the ocular surface is the tear fluid, and its main source is this bit of 'dull' glandular tissue termed the lacrimal gland. In the ancient literature it was assumed, according to Duke-Elder, that the tears emanated from the brain. This is not quite true as we know now but it indicates the high appreciation that the tears have enjoyed already in ancient times. Tears are a complex mixture of water, salts, nutrients, mucins, protective innate antimicrobial factors and specific IgA antibodies, cytokines, chemokines, growth factors, hormones and a plethora of other factors that are not yet identified [13, 14]. These ingredients indicate that the tears are involved in a multitude of essential processes at the ocular surface ranging from wetting, preservation of tissue integrity and regulation of cell differentiation and immune response to formation of an ideal precorneal optical interface. The adequate volume and composition of the tear fluid are hence key elements of ocular surface well-being, and the investigation of lacrimal gland function is a key issue in ocular surface research.

However, the analysis of the tear fluid is hampered by a few complicating features. One is the fact that the actual preocular tear film on the cornea and conjunctiva is derived not only from the lacrimal gland, but also from other secretory elements either located directly inside the conjunctiva (goblet cells and fluid transport across the conjunctival epithelial cells) or related to the conjunctiva (accessory lacrimal glands and the tarsal glands of Meibom). On the other hand, the preocular tear film as such is inhomogeneous in nature and is split into at least two fractions, leading to a 'two-compartment model' [15] of the preocular tear film, which consists of the very thin but highly relevant precorneal layer and of the tear reservoir at the meniscus. Both are mixed and recalibrated with every blink but separated and increasingly different due to evaporation or other environmental factors during gaze with opened interpalpebral fissure. To make it even more complicated, another important feature occurs in the closed eye. Comparison of the tear fluid composition with conventional [16] and newly developed ultrasensitive techniques [14] has given evidence that it changes in a kind of diurnal fashion. During sleep when the eyelids are closed and the secretion from the lacrimal gland has almost ceased, the preocular tear film drastically changes its composition towards a proinflammatory microenvironment within the moist chamber of the closed retropalpebral space. These observations led to the development of a 'closed-eye model' [16] of the preocular tear film which has greatly aided our understanding of the functional plasticity of the tears and of the different approaches of the ocular surface towards immune defense [3, 14].

Due to the reasons explained above, tear collection at the preocular level does not necessarily reflect the production parameters of the lacrimal gland. The precise analysis of the tear fluid and its changes depending on the defined experimental supply of the lacrimal gland with mediators that influence secretion is therefore an important element of lacrimal gland research but has proven difficult with currently available methods.

Advances in Monitoring Lacrimal Gland Function

In order to correctly monitor lacrimal gland function, Ding et al. [2] report an important technical improvement. In the rabbit model, they do not only cannulate the

excretory lacrimal duct to obtain pure tears from one lacrimal gland, which has been used previously [17], but they combine this handy technique of separate unilateral tear collection with a sophisticated approach to also stimulate the lacrimal gland in a defined strictly unilateral manner. For this purpose, a plastic tube is introduced through a tiny insertion of the lower fornical conjunctiva and placed into the connective tissue compartment directly overlying the rabbit inferior lacrimal gland. By this approach, it is possible to perform pharmacological stimulation of a single lacrimal gland, for example with different secretagogues, and to compare the differential effect. This offers great advantages over the standard procedure of systemic application of mediators and is able to achieve a higher sensitivity (lower dosage of mediators), an effectively stronger response and it avoids systemic side effects that can be deleterious to the individual and can also interfere with tear production.

Conclusion

This new method for selective stimulation of a single gland in situ combined with the known unilateral tear collection via excretory duct cannulation, which can both most likely also be applied to other species, opens the door for a more detailed analysis of lacrimal gland function. This is a prerequisite for advances in a whole range of ocular surface alterations, in particular those that show any changes of the tear fluid.

References

1 Bron AJ, Tripathi DM, Tripathi BJ: Wolff's Anatomy of the Eye and Orbit. London, Chapman & Hall Medical, 1997.
2 Ding C, Rife L, Nakamura T, Wang YW, Kopp K, Schechter JE: A novel, local technique for studying rabbit lacrimal gland secretion in situ. Ophthalmic Res 2008;40:49–52.
3 Knop E, Knop N: Anatomy and immunology of the ocular surface; in Niederkorn JY, Kaplan HJ (eds): Immune Response and the Eye, ed 2. Basel, Karger, 2007, pp 36–49.
4 Stern ME, Beuerman RW, Fox RI, Gao J, Mircheff AK, Pflugfelder SC: A unified theory of the role of the ocular surface in dry eye. Adv Exp Med Biol 1998;438:643–651.
5 Pflugfelder SC, Stern ME: Future directions in therapeutic interventions for conjunctival inflammatory disorders. Curr Opin Allergy Clin Immunol 2007;7:450–453.
6 Knop E, Knop N: A functional unit for ocular surface immune defense formed by the lacrimal gland, conjunctiva and lacrimal drainage system. Adv Exp Med Biol 2002; 506:835–844.
7 Knop E, Knop N: The role of eye-associated lymphoid tissue in corneal immune protection. J Anat 2005;206:271–285.
8 Stern ME, Pflugfelder SC: Inflammation in dry eye. Ocul Surf 2004;2:124–130.
9 McDermott AM, Perez V, Huang AJ, et al: Pathways of corneal and ocular surface inflammation: a perspective from the Cullen symposium. Ocul Surf 2005;3:S131–S138.
10 Knop E, Knop N: Influence of the eye-associated lymphoid tissue (EALT) on inflammatory ocular surface disease. Ocul Surf 2005; 3:S180–S186.
11 Mircheff AK, Wang Y, Jean MS, Ding C, Trousdale MD, Hamm-Alvarez SF, Schechter JE: Mucosal immunity and self-tolerance in the ocular surface system. Ocul Surf 2005; 3:182–192.
12 Niederkorn JY, Stern ME, Pflugfelder SC, De Paiva CS, Corrales RM, Gao J, Siemasko K: Desiccating stress induces T cell-mediated Sjögren's syndrome-like lacrimal keratoconjunctivitis. J Immunol 2006;176:3950–3957.
13 Sullivan DA: Immunology of the lacrimal gland and tear film. Dev Ophthalmol 1999; 30:39–53.
14 Sack RA, Conradi L, Krumholz D, Beaton A, Sathe S, Morris C: Membrane array characterization of 80 chemokines, cytokines, and growth factors in open- and closed-eye tears: angiogenin and other defense system constituents. Invest Ophthalmol Vis Sci 2005; 46:1228–1238.
15 Bron AJ, Tiffany JM, Yokoi N, Gouveia SM: Using osmolarity to diagnose dry eye: a compartmental hypothesis and review of our assumptions. Adv Exp Med Biol 2002;506: 1087–1095.
16 Sack RA, Beaton A, Sathe S, Morris C, Willcox M, Bogart B: Towards a closed eye model of the pre-ocular tear layer. Prog Retin Eye Res 2000;19:649–668.
17 Petounis AD, Akritopoulos P: Influence of topical and systemic beta-blockers on tear production. Int Ophthalmol 1989;13:75–80.