

Topical tear stimulation—a new insight for dry eye therapy

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Comment on: Nakamachi T, Ohtaki H, Seki T, *et al.* PACAP suppresses dry eye signs by stimulating tear secretion. *Nat Commun* 2016;7:12034.

Abstract: Dry eye disease is the most prevalent ocular surface disease in eye clinics. The deficiency of tears is regarded as one of the main pathogenic factors for this disease. Due to the fact that the components of tears are still far beyond our knowledge, the restoration of physiological tears remains the optimum choice for dry eye patients. However, the traditional way to stimulate tear production by systemic administration of muscarinic agonists usually encounters severe side effects. Recently, Nakamachi and colleagues reported that PACAP, a native neurotransmitter present in tear fluid, could stimulate main lacrimal gland secretion and relieve dry eye-like symptoms in PACAP knockout mice. The finding of PACAP and its underlying mechanisms suggest a new modality for dry eye treatment via targeted topical tear stimulations.

Keywords: Dry eye; tear stimulation; lacrimal gland; PACAP

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Tears are merely regarded as the sign of sadness or happiness in the knowledge of ordinary people, yet it is actually an indispensable component to maintain ocular surface homeostasis. In addition to its role as a lubricant, tear film also contributes to proper refraction, corneal epithelium health, and ocular immunization barrier. The impairments of the quantity, quality or hydrodynamics of tears lead to dry eye disease (DED), which has become the most prevalent disease in ophthalmic clinics. Epidemiological studies showed that the incidence of DED ranges from 5% to 35% all over the world. In China, the incidence of DED is higher than that in Europe or US, almost up to 21–30%. Thus, how to relieve the symptoms and improve the life quality of dry eye patients become a hot topic for ocular drug development.

The term “dry eye” gives the impression that DED is exclusively caused by dryness, but the aetiology is far more complicated. Ocular desiccation is not the sole pathogenic mechanism involved in DED. As a result, prevention of desiccation alone is inadequate to manage the condition.

More than as an electrolyte solution, tears also contain bioactive molecules, such as various growth factors, mucins, lipids, vitamins, etc., which explains the frequently encountered limitations of artificial tears that only serve to increase ocular surface wetness. Moreover, in the course of DED development, the deficiency of tears also leads to inflammatory responses, partially due to the loss of anti-inflammatory factors contained in tear fluids on ocular surface, which is corroborated by the fact that self-serum achieves better treatment efficacies. Thus, the restoration of physiological tear secretion should be more critical than supplement of other palliatives if lacrimal function is retained.

Historically, the application of therapies stimulating tear production by systemic administration of muscarinic agonist was limited due to their side effects (1). For instance, oral muscarinic agonists, such as pilocarpine or cevimeline, have been used to promote lacrimal secretion by activating cholinergic signal transduction pathway in lacrimal acinar cells, but are associated with sweating and diarrhea, and may additionally cause accommodative spasm and brow ache in

young patients.

Topical purinergic receptor agonist that stimulates transconjunctival water flow and mucin secretion from conjunctival goblet cells is a new treatment modality for dry eye. DIQUAS ophthalmic solution 3% (generic name: diquafosol tetrasodium) has been commercially available since 2010. Diquafosol tetrasodium is an agonist of P2Y₂ receptor (2), which is a member of the family of G-protein coupled receptors, and an alternative chloride channel (3). Until now, at least eight different clinical studies have suggested that diquafosol exhibits therapeutic efficacies and good tolerability in various types of dry eye patients (4).

Recently, Nakamachi and colleagues reported in *Nature Communication* that PACAP, a neurotransmitter present in tear fluids, could stimulate lacrimal gland secretion via PAC1-R/cAMP/PKA/AQP5 signaling. Topical administration of PACAP eye drops increased tear meniscus height, improved corneal fluorescein staining and relieved dry eye symptoms in PACAP knockout mice (5). Strikingly, topical application of PACAP was suggested to directly stimulate main lacrimal gland secretion via nerve action (5). Compared with diquafosol, the underlying signaling of PACAP in main lacrimal gland was clearly dissected in this recent report, which not only sharpens our understanding of neuromodulation of tear secretion, but also facilitates chemical leads screening in ophthalmic pharmaceuticals.

Although the stimulation of tear secretion from lacrimal gland is a new direction, it requires the premise that lacrimal gland is functional, which at least can receive nerve impulses and secrete tears. However, in certain dry eye patients, such as some Sjögren's syndrome (SS) dry eye patients, when the basic function of their lacrimal glands is lost, PACAP may not be applicable. Fortunately, we know that tears could be produced from accessory lacrimal gland, goblet cell and meibomian gland as well. Previous studies showed that PACAP and its receptor are present in other parts of ocular surface (6). Thus, the function of PACAP on ocular surface, especially in accessory lacrimal gland, goblet cell and meibomian gland, is worth further exploration. Indeed, vasoactive intestinal polypeptide (VIP) can increase mucin production in conjunctival goblet cells via the stimulation of parasympathetic nerves (7,8). Therefore, we can speculate that PACAP, as a member of the VIP family, may also contribute to mucin production.

PACAP provides a new insight for tear stimulation treatment in DED. We are eager to see its clinical safety, ocular tolerability and therapeutic efficacies in dry eye patients. The finding of PACAP is the fruit of our in-depth

understanding of tear physiology, which opens a new window for anti-dry eye drug development. However, the complexity of the structure and function of tear film is still far beyond our knowledge. A more comprehensive recognition of the process of tear production will accelerate the development of more effective DED therapies by stimulating tears.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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