Discussion. The implantable system described in this report provides a method for delivering aqueous solutions to the external rabbit eye for at least 6 weeks. The PTFE tube is implanted in the superior conjunctival fornix 4 weeks prior to the implantation of the pump. During this time fibrous tissue ingrowth secures the tube firmly to the surrounding tissues. By allowing the tube to be anchored by fibrous tissue ingrowth, problems with extrusion or retraction are largely eliminated. The tube appears to be well tolerated, and the present system can be refilled repeatedly without surgical intervention or manipulation of the ocular tissues. This reduces the risk of inflammation and infection at the pump sites.


Key words: implantable, pump, continuous delivery, polytetrafluoroethylene tube, transconjunctival tube

REFERENCES


Mechanisms responsible for regulation of tear film mucus are poorly understood. Humoral factors responsible for stimulation of mucus secretion can be studied in vitro by using the free-swimming urn cell, a normal component of the coelomic fluid of the marine invertebrate Sipunculus nudus. With this system, a tear mucus-stimulating factor was found in normal human tears but was markedly decreased in patients with dry eye syndromes. It is suggested that a mucus-stimulating factor exists in normal human tears and that a decrease in this substance may be instrumental in the pathophysiology of certain dry eye syndromes.

Abnormalities in mucus and its production are characteristic of various diseases, especially prominent in such conditions as cholera and mucoviscidosis. Endogenous mechanisms responsible for mucus stimulation are not well understood and could contribute to the pathogenesis of some diseases.1,2 In mammalian systems, goblet cells responsible for production of mucus along membranes may respond, at least in part, to nonneural factors.1 Evidence has been presented describing a polypeptide factor in patients with cystic fibrosis interfering with ciliary activity,1,2 which reflects alterations in the overlying mucus layer.1,2 Recently, a macromolecule has been found in the sera and secretions of patients with cystic fibrosis as well as in normal patients, capable of stimulating the urn system, a noninnervated mucus-secretory cell system.4 The present study examined the ability of this mucus-secretory cell system to detect mucus-secretory substances (MSSs) in tears and raises the question of the existence of regulatory factors for tear mucus production.

Methods. The assay system for MSS uses the
Table I. Urn cell stimulation by lacrimal fluid

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Mean ± S.E.M.*</th>
<th>Range</th>
<th>p value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ocular pemphigoid (2)</td>
<td>3.0 ± 0</td>
<td>3.0</td>
<td>&lt;0.02</td>
</tr>
<tr>
<td>Stevens-Johnson syndrome (3)</td>
<td>2.2 ± 0.5</td>
<td>1.4-3.0</td>
<td>&lt;0.002</td>
</tr>
<tr>
<td>Keratoconjunctivitis sicca (4)</td>
<td>2.3 ± 0.3</td>
<td>1.5-3.0</td>
<td>&lt;0.002</td>
</tr>
<tr>
<td>Normal (18)</td>
<td>5.2 ± 0.1</td>
<td>4.0-6.0</td>
<td></td>
</tr>
</tbody>
</table>

*See Methods for unit.
†vs. normal by Mann-Whitney U test, two tail.
†No. of patients in parentheses.

free-swimming urn cells from the coelomic fluid of the marine invertebrate Sipunculus nudus. The scavenger cells function in vivo by producing long mucus tails in response to defined stimuli. Foreign debris, pathogens, and dead cells become trapped and then excreted from the animal.

Urn cells are maintained in vitro in the supernatant fluid of S. nudus whole blood (coelomic fluid) at 4° C. The test is performed by mixing 5 /µl of test substance and 5 /µl of urn cell fluid (approximately 50 to 100 urn cells) in a depression slide at 22° C. If the test substance contains an MSS, a tail of mucus is induced on the urn cells, and the length of tails is measured with a micrometer eye piece in a light microscope. The average length of 30 tails after a given time (usually 20 min) is expressed in multiples of the average length of the urn cell vesicle (approximately 70 µm).

Tears were collected from 18 normal human volunteers. A blunt end of a white blood cell diluting pipette was touched to the tear meniscus without rubbing the conjunctiva, and 10 to 100 /µl of fluid were collected. No effort was made to induce tear production. Nine patients with various "dry eye" conditions were also examined. Samples were stored at -70° C until tested.

A pool of normal tears was dialyzed in cellophane membranes against several changes of an excess of filtered (Millipore filter, 0.45 µm) seawater. The retentate was then compared with the starting pool in the urn cell assay.

Individual tear samples were heated in sealed glass tubes to 85° C for 5 min in order to test temperature sensitivity.

Results. All tear samples from normal individuals gave urn scores (tail lengths) between 4 and 6 (Table I). In some instances, samples were rerun with similar results. All three groups of patients with ocular disorders showed highly significant lower levels of MSS activity when compared to normals (Table I). The MSS from normal tears did not dialyze through cellophane membranes after 5 days.

Tear samples from normal volunteers could be titered to 1:32 before losing activity, and heating at 85° C for 5 min did not destroy the stimulating activity.

Discussion. The present study examined the ability of human tears to stimulate an invertebrate mucus-secreting cell. Previous studies demonstrated the ability of the urn cell to respond to sera and other biological fluids from patients with cystic fibrosis as well as from normal subjects. The present study again demonstrated the activity in tears from normal patients to stimulate mucus production by the urn cell and, in addition, showed that patients with certain dry eye syndromes have low levels of this activity.

Mucus represents a major component of normal tears and acts as a wetting agent over the corneal epithelial surface. Decreased goblet cell numbers, as well as diminished tear film stability, have suggested that mucus deficiency might represent a primary cause of ocular change. Whether such primary disorders exist remains speculative, but they could result from failure of a local stimulus to the goblet cells.

The mechanism of control of mucus secretion in ocular as well as nonocular structures is unclear and may depend on both nervous and chemical stimulation. A substance has been found in the serum and in the medium from skin fibroblast cultures from patients with cystic fibrosis. Its activity is assayed by its effect on the movement of ciliated epithelium from rabbit trachea and oyster gills, which directly reflects changes in the overlying mucus layer. Recently the urn cell assay has demonstrated MSSs in sera and certain secretions from patients with both cystic fibrosis and cholera. These early studies suggested that the urn system offered a method capable of identifying molecules responsible for regulation of mucus secretory systems, unencumbered by the problems...
of the highly subjective bioassays previously employed.  

That MSS in tears reflects part of a normal physiological mechanism is supported by an absence or low levels of this activity in patients with Stevens-Johnson syndrome and ocular pemphigoid—mucus deficiency diseases. Curiously, keratoconjunctivitis sicca patients, known to have primarily an aqueous tear-layer deficiency, also demonstrated low levels of MSS in their tears. It is possible that the activity originates with aqueous tear components in the lacrimal gland and remains at a constant concentration. Since the assay is performed at a constant tear volume, the amount of aqueous tear examined would be extremely low.

The tear substance responsible for the stimulation in this system could reside with any of the nondialyzable tear macromolecules. Whether the MSS activity resides with a previously described tear macromolecule must await separation of tear components and isolation of the active fraction.

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Key words: mucus, urchin cell, tears, invertebrate, secretion, ocular pemphigoid

REFERENCES


Cone threshold vs. retinal eccentricity: changes with dark adaptation. BRUCE DRUM.

Detection threshold vs. retinal eccentricity functions measured during the cone plateau of the dark-adaptation curve differed from comparable functions measured on a uniform photopic background. Dark adaptation increased parafoveal sensitivity more than either foveal or peripheral sensitivity.

The variation of cone sensitivity over the visual field in the presence of a uniform photopic background is well known; sensitivity falls off rapidly in the parafovea from a sharp foveal peak, then declines more gradually toward the periphery. The slope of the eccentricity function is steeper for small targets than for large targets. Comparable cone data for dark-adapted conditions are difficult to obtain because the rods present in the extrafoveal retina are normally more sensitive. Because cones dark-adapt faster than rods, however, there is a period of several minutes after the extinction of a strong adapting light, known as the cone plateau, during which cones are completely dark-adapted but rods are still relatively insensitive. Using a white circular test target with a 1° visual angle and a 1 sec duration, Sloan showed that cone thresholds are higher for large targets than for small targets. Comparative cone data for dark-adapted conditions are difficult to obtain because the rods present in the extrafoveal retina are normally more sensitive. Because cones dark-adapt faster than rods, however, there is a period of several minutes after the extinction of a strong adapting light, known as the cone plateau, during which cones are completely dark-adapted but rods are still relatively insensitive.

Using a white circular test target with a 1° visual angle and a 1 sec duration, Sloan measured cone thresholds during the cone plateau as a function of eccentricity and compared the results to a similar light-adapted cone (LAC) function for which the adapting luminance was 2.23 cd/m². The shapes of the LAC and DAC functions did not differ significantly for her single normal subject.

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