pup was day blind, many cones in the dog appeared normal.

Cytoplasmic accumulation of filaments or tubules in degenerating neurons (neurofibrillar degeneration; NFD) has been found in the cortical neurons of human patients with Alzheimer’s disease as well as in cortical neurons of experimental animals treated with aluminum compounds or mitotic spindle inhibitors. The fibrillar structures present in these neurons as well as in the cones of hemeralopic dogs may represent a nonspecific structural manifestation of neuronal degeneration. By virtue of having filaments accumulating in the cytoplasm of degenerating cones, hemeralopia in dogs is a NFD. It is tempting to compare the morphologic features of hemeralopia in dogs to those found in rod monochromatism in man. The paucity of anatomic data in the latter makes such comparison difficult. In the three human cases that to our knowledge have been reported, all examinations were made by light microscopy, and in only one case was the tissue freshly fixed. Even that case was complicated by the presence of concomitant intractable glaucoma. In the human studies, Larsen reported the retina to be generally normal both in structure and number of rods and cones, except at the central fovea. Here the receptors were short and plump, and had either shortened outer limbs or none at all. In the case of Harrison, Hoefnagel, and Hayward, there were imperfectly shaped squat cone-like units and considerable thinning of the outer nuclear layer with marked diminution in the number of cone nuclei. In the macula of that case, the photoreceptor layer had almost entirely disappeared. The last case, reported by Falls, Wolter, and Alpern, had no foveola, but the foveal retina had densely arranged cones of the foveal type, and their number and appearance seemed to be normal. Cone inner segments and nuclei were missing nasal to the optic disc, but the retina between the disc and fovea had a few well developed cones. Ectopic cone nuclei such as we found in the six-month-old hemeralopic dog were common in foveal and extrafoveal areas.

To compare the canine rod monochromatism to that in man is difficult. The wide disparity in the findings in the human cases suggest that, at least structurally, more than one disease entity may be represented.

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Key words: dog, hemeralopia, cone degeneration, neurofilaments, inherited disease, neurofibrillar degeneration, rod monochromatism.

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Fenoprofen and ocular prostaglandin production. STEVEN M. FODOS AND BERNARD BECKER.

The ocular effect of fenoprofen, a new nonsteroidal anti-inflammatory agent, was studied. The elevations of intraocular pressure and aqueous humor protein induced by 5 per cent arachidonic acid applied to rabbit eyes were partially blocked by topical pretreatment with 2 per cent fenoprofen. Fenoprofen 2 per cent did not prevent the elevation of intraocular pressure produced by 3 μg of prostaglandin E. The results implied that fenoprofen inhibits the in vivo synthesis or release of ocular prostaglandin.
Fenoprofen, dl-2-(3-phenoxypyphenyl) propionic acid, has been described as an effective nonsteroidal anti-inflammatory agent.\(^1\) A topical preparation of fenoprofen sodium 1 per cent was found to be an effective therapy for uveitis induced in rabbits.\(^3\) Fenoprofen also had analgesic properties.\(^1\)

Inhibition of prostaglandin synthesis has been suggested as the mechanism of action of many nonsteroidal anti-inflammatory drugs, such as indomethacin and aspirin.\(^4\) Indomethacin pretreatment also prevented the elevation of intraocular pressure and the increased aqueous humor protein induced by the administration of topical arachidonic acid, a prostaglandin E\(_2\) (PGE\(_2\)) precursor, but failed to block the similar effects of PGE\(_2\) itself.\(^5\) This suggested an inhibitory action of indomethacin on ocular prostaglandin synthesis. Indomethacin and aspirin are poorly soluble compounds. Aspirin given topically did not block the arachidonic acid-induced intraocular pressure elevation (unpublished results), whereas topical instillation of indomethacin suspensions did have an inhibitory effect on this system.\(^5\) As fenoprofen is water soluble, it might have distinct advantages as a topical agent. Therefore, similar studies were carried out as to the effect and mode of action of fenoprofen in the eye.

Adult albino rabbits were restrained. Intraocular pressure was measured with a Mackay-Marg tonometer utilizing 0.5 per cent proparacaine anesthesia. Fenoprofen sodium was freshly prepared in aqueous solution, without buffer or preservative, in concentrations of 1 per cent, 2 per cent (pH 7.0), and 5 per cent. Two drops were instilled in one eye and diluent in the other eye of each animal. Equal numbers of right and left eyes were used. Thirty minutes later intraocular pressure was remeasured (0 minute). Two drops of freshly prepared arachidonic acid 5 per cent (Sigma Chemical Co., St. Louis, Mo.) in peanut oil were applied to both eyes of all animals. Repeat intraocular pressure measurements were made at 0, 15, 30, 60, 120, and 240 minutes thereafter. The same protocol was repeated with 2 per cent fenoprofen solution but 30 minutes after administration of arachidonic acid, intraocular pressure was measured and anterior chamber aqueous humor was removed from both eyes. Determination of protein was carried out.\(^2\) Similar experiments were performed testing the effect of fenoprofen 2 per cent against the intraocular pressure elevation induced by 3 \(\mu\)g of topically administered PGE\(_2\). Each milligram of PGE\(_2\) was dissolved in 0.1 ml. of 95 per cent ethanol and 0.9 ml. of 0.02 per cent sodium carbonate aqueous solution.

The elevation of intraocular pressure induced by arachidonic acid was partially blocked by topical pretreatment with fenoprofen (Table I). Thirty minutes after arachidonic acid application to both eyes of 16 rabbits, the mean intraocular pressure of the 2 per cent fenoprofen-pretreated eyes (17.5 ± 2.4 (S.D.) mm. Hg) was significantly (\(p < 0.01\)) lower than that of the diluent-treated eyes of the same animals (22.3 ± 4.9 mm. Hg). Similar results were obtained with the 5 per cent solution of fenoprofen but the 1 per cent solution was less effective.

Thirty minutes after the topical administration of 5 per cent arachidonic acid to both eyes of 8 rabbits, the mean aqueous humor protein in eyes pretreated with 2 per cent fenoprofen was 8.3 ± 5.4 (S.D.) mg. per milliliter, significantly (\(p < 0.001\)) less than the value for control fellow eyes pretreated with diluent, 17.0 ± 7.3 mg. per milliliter. Fenoprofen 2 per cent did not prevent the elevation of intraocular pressure produced by PGE\(_2\) administered topically to eight rabbits (Table II). At 30 minutes after 3 \(\mu\)g of PGE\(_2\), the mean intraocular pressure of 2 per cent fenoprofen-pretreated eyes was 27.6 ± 5.9 mm. Hg as compared to 26.4 ± 5.9 mm. Hg for diluent-pretreated fellow eyes.

Thus, fenoprofen has an action on the eye similar to aspirin and indomethacin. The results imply that this nonsteroidal anti-inflammatory drug inhibits the in vivo synthesis or release of ocular prostaglandin. As compared to studies with systemically administered indomethacin, the block is not complete with the concentrations of topically administered fenoprofen used as evidenced by some rise of intraocular pressure and increase of aqueous humor protein in the present study. The effect of 2 per cent fenoprofen solution is similar to that of 0.5 per cent indomethacin suspension.\(^6\) The pH of our solution is 7.0. Since there is evidence that more acidic solutions may be more effective,\(^3\) pH adjustment should be investigated in future studies of topical fenoprofen.

As PGE is implicated in the mediation of the inflammation of uveitis in both rabbits and humans,\(^7\) and fenoprofen is effective against rabbit uveitis,\(^3\) trials of this drug in human uveitis are indicated. It is also of interest that other propionic acid derivatives block the in vitro synthesis of prostaglandin.\(^9\) These are not available as ophthalmic preparations but should be studied in comparison to fenoprofen.

Oxyphenbutazone 10 per cent ophthalmic ointment (Tanderil) is another currently formulated nonsteroidal anti-inflammatory drug which partially blocks the intraocular pressure effects of arachidonic acid. Thirty minutes after 5 per cent arachidonic acid, the mean intraocular pressure in eight rabbit eyes pretreated with Tanderil was 21.9 ± 5.5 (S.D.) mm. Hg versus 27.1 ± 6.4 mm. Hg in diluent-treated fellow eyes (previously unpublished results).

In contrast, no significant block of 5 per cent arachidonic acid-induced ocular hypertension is accomplished by pretreating rabbit eyes with
Table I. Effect of topical fenoprofen on the intraocular pressure response to arachidonic acid

<table>
<thead>
<tr>
<th>Arachidonic acid 5% O.U.</th>
<th>No. of rabbits</th>
<th>Mean intraocular pressure ± S.D. (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>0 min.</td>
</tr>
<tr>
<td>Fenoprofen 1%</td>
<td>8</td>
<td>16.6 ± 1.6</td>
</tr>
<tr>
<td>Diluent</td>
<td></td>
<td>16.8 ± 1.4</td>
</tr>
<tr>
<td>Fenoprofen 2%</td>
<td>10</td>
<td>14.8 ± 1.5</td>
</tr>
<tr>
<td>Diluent</td>
<td></td>
<td>15.1 ± 1.7</td>
</tr>
<tr>
<td>Fenoprofen 5%</td>
<td>8</td>
<td>15.5 ± 1.2</td>
</tr>
<tr>
<td>Diluent</td>
<td></td>
<td>15.8 ± 0.5</td>
</tr>
</tbody>
</table>

*Significant difference between the eyes of individual rabbits receiving fenoprofen to one eye and diluent to the other eye, paired t test, p < 0.02.

f Significant difference between the eyes of individual rabbits receiving fenoprofen to one eye and diluent to the other eye, paired t test, p < 0.01.

Table II. Effect of topical fenoprofen on the intraocular pressure response to PGE₂

<table>
<thead>
<tr>
<th>PGE₂ (3 μg) O.U.</th>
<th>No. of rabbits</th>
<th>Mean intraocular pressure ± S.D. (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>0 min.</td>
</tr>
<tr>
<td>Fenoprofen 2%</td>
<td>8</td>
<td>12.4 ± 1.3</td>
</tr>
<tr>
<td>Diluent</td>
<td></td>
<td>12.6 ± 1.1</td>
</tr>
</tbody>
</table>

dexamethasone 0.1 per cent drops. Yet, corticosteroids are very effective in the treatment of most oculocutaneous inflammatory diseases. This suggests that corticosteroid therapy inhibits mediators of inflammation in the eye other than the prostaglandins. Certain clinical entities manifested by breakdown of the blood-aqueous barrier may be prostaglandin-mediated. The discovery of new nonsteroidal anti-inflammatory drugs may provide specific therapy for these conditions and, in addition, obviate the deleterious side effects of corticosteroid administration.

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Key words: fenoprofen, nonsteroidal anti-inflammatory agent, prostaglandin synthesis.

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