The numbers of FcR in the various tissues did not correlate with the numbers of PFC in the same tissues. Splenic FcR remained fairly constant and probably included rosettes formed by neutrophils and macrophages. The numbers of FcR in the uveal tract were about the same as those seen in normal rabbit uveal tissue and could reflect the fact that in most cases there was little or no uveal reaction. The considerable variation in the percentages of conjunctival FcR is probably due to the variation in the numbers of neutrophils present in the inflamed conjunctival tissue. Neutrophils are known to possess FcR. FcR have not been described in mucosa-associated lymphoid tissue, but cells bearing a thymic antigen and cells with heavy chain markers have been described in rabbit bronchial-associated lymphoid tissue. Since some T lymphocytes have FcR, we might assume that some of the conjunctival FcR are T lymphocytes.

Chandler and Axelrod suggested that after processing of antigen by CALT, antibody, possibly secretory IgA, is produced by cells that "home" to the lacrimal gland. They suggested that secretory antibody might be found in the tears. Our results showed that at least some of the serum antibody is produced by conjunctival and limbal plasma cells. Further experiments will show whether the conjunctival and limbal PFC produce IgA antibody, whether lacrimal gland lymphocytes participate in antibody production, and whether IgA antibody is present in the tears.

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Key words: topical immunization, plaque-forming cells, conjunctival PFC, hemagglutination titers, Fe receptor cells

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Suppression of adrenergic adaptation in the eye with a prostaglandin synthesis inhibitor. R. MICHAEL DUFFIN, ROBERT E. CHRISTENSEN, AND MICHAEL V. W. BERGAMINI.

The treatment of glaucoma patients with a topical medication is sometimes associated with adaptation (the development of subsensitivity) to the effect of the medication. In the rabbit eye, adaptation develops when nor-epinephrine is administered topically on a daily basis. A marked decrease in the intraocular pressure is observed the first day, but diminishing responses are observed on subsequent days. Since prostaglandins may be released in response to catecholamines and have been found to inhibit adrenergic neurotransmission, we treated rabbits with topical flurbiprofen, a potent cyclooxygenase (prostaglandin synthesis) inhibitor, to suppress adaptation to norepinephrine. The results demonstrate a significant suppression of adaptation in the concentration range of 0.001% to 0.1% flurbiprofen (p < 0.0005). This finding...
supports the theory that cyclooxygenase products mediate the development of adaptation to exogenous norepinephrine in the rabbit eye. (INVEST OPHTHALMOL VIS SCI 21:756-759, 1981.)

During medical treatment of chronic open-angle glaucoma, some patients seem to become less sensitive to the hypotensive effect of the topical medication. Although this phenomenon may represent a worsening of the glaucoma or a compliance problem, a physiologic subsensitivity to the medication is sometimes suspected.

Norepinephrine (NE) has been used on a limited basis to treat glaucoma.1 2 We have observed that repeated daily doses of NE in rabbits results in significant adaptation of the ocular hypotensive response after 2 or 3 days. The term adaptation is used to describe a diminished effect after repeated doses of a drug, without the determination that the decrease in response is caused by tolerance or tachyphylaxis. In the cat, indomethacin was found to prevent acute tolerance to the pressor response to systemic NE.3 Likewise, indomethacin abolished the induction of tachyphylaxis to the beta-agonist, isoproterenol, in guinea pig airway smooth muscle.4 The purpose of this study is to investigate the mechanism of the acute development of adaptation in the rabbit eye with the use of flurbiprofen, a potent water-soluble prostaglandin synthetase inhibitor.

Materials and methods. A total of 24 New Zealand albino rabbits (2.5 to 3.5 kg, male and female) were tested in this study. Before drug treatment, the eyes were carefully examined with a penlight and no detectable ocular inflammation or abnormality was found. The baseline intraocular pressure (IOP) values were symmetric in each animal. The Alcon Pneumatonograph was used for all IOP measurements after administration of one drop of proparacaine HCl 0.5%.

After an IOP measurement, six rabbits received two drops (approximately 50 μl each) of topical NE 2% given 5 min apart to one eye and vehicle treatment to the contralateral eye. Bilateral IOPs were monitored at 1, 3, 5, 7, and 24 hr after NE treatment, with the contralateral IOP as the control for individual variability and diurnal variation. Langham and Palewicz5 found the maximal decrease of IOP was 3 to 5 hr after NE treatment. NE was administered every 24 hr for 5 days, and the IOP was monitored daily at the intervals given above.

Three other groups with six rabbits each received NE 2% to the treated eye every 24 hr for 5 days. One group also received one drop (approximately 50 μl) of flurbiprofen 0.1% to the NE-treated eye four times a day (about every 6 hr) beginning 24 hr before the initial NE treatment and continuing to the end of the 5 day course. IOP was measured daily at 3, 5, 7, and 24 hr after NE treatment. Because of the possibility of systemic absorption of flurbiprofen, vehicle was not given to the contralateral eye. Instead, the control consisted of a separate group of six animals that received identical treatment, except for the substitution of vehicle for flurbiprofen.

The final group of six rabbits was treated with flurbiprofen 0.001% and NE 2% exactly as explained above. After a 2 week wash-out period, flurbiprofen 0.01% was tested with NE 2% in the same animal group. The data were analyzed for statistical significance with the unpaired, one-tailed Student’s t test.

Drug preparation. Norepinephrine ascorbate 2% aqueous solution was prepared fresh weekly (L-arterenol, anhydrous L-ascorbic acid, Sigma Chemical Co., St. Louis, Mo.). The pH was adjusted to 6.2 with sodium hydroxide and the solution was sterilized with passage through a milli-
Fig. 2. Dose-response data for the degree of suppression of adrenergic adaptation by various concentrations of flurbiprofen (0.001%, 0.01%, and 0.1%). Each point represents the mean ± S.E.M. of the maximal IOP difference between treated and untreated rabbit eyes on the fifth day of a 5 day course of daily topical 2% NE. Note that the higher concentrations of flurbiprofen allow a greater decrease in IOP, i.e., suppress adaptation to a greater degree.

Results. Topical flurbiprofen produced no conjunctival hyperemia or corneal clouding by penlight examination during the 6 day treatment course. Flurbiprofen alone did not change the IOP in 12 animals over a 24 hr period. NE induced a mild conjunctival hyperemia that lasted for several hours but was usually gone the next day.

Daily topical treatment with NE alone or with NE plus flurbiprofen vehicle produced virtually identical responses; therefore only the latter data are plotted (see Fig. 1, control). A maximal ocular hypotensive response occurred the first day but diminished on subsequent days. The maximal pressure difference was usually observed 5 hr after NE treatment but sometimes occurred at the 3 or 7 hr measurement. Because of the importance of documenting the maximal IOP response and because of the variable time courses between animals, the maximal responses were compared whenever they occurred rather than at one particular time.

In the group of animals treated with NE alone, a mean rise in IOP relative to control eyes was seen 1 hr after NE administration each day. This early pressure rise was minimal the first day but gradually increased to 6.3 ± 0.8 mm Hg (mean ± S.E.M.) above baseline on the fifth day. This biphasic IOP response to NE agrees with the results of previous studies.\(^5\)\(^6\)

Treatment with flurbiprofen 0.01% inhibited the development of adaptation. As shown in Fig. 1, there was maximal hypotensive response on day 1, and following days showed only slightly decreased responses. The difference between the treated and control responses was statistically significant on day 2 (\(p < 0.0005\)) and on day 5 (\(p < 0.01\)).

Flurbiprofen 0.001% produced a statistically significant effect on day 2 (\(p < 0.025\)) but not on day 5 (\(p < 0.10\)). The 0.1% concentration suppressed adaptation in a comparable manner to the 0.01% concentration (\(p < 0.005\) on day 5). The mean IOP of the untreated eyes represented by the four curves of Fig. 1 remained relatively stable at approximately 22 ± 1 mm Hg, with no consistent upward or downward trend during the 5 day course.

Fig. 2 shows the dose-response data for the various concentrations of flurbiprofen on the fifth experimental day. The maximal effective concentration of flurbiprofen probably lies between 0.01% and 0.1%, since the ocular hypotensive response with these concentrations approached the maximal response possible with NE 2% alone. The control group (vehicle treated) showed no inhibition of adaptation to NE (Fig. 1).

Discussion. To understand the possible mechanisms of adrenergic adaptation, it is helpful to briefly review the relationship between catecholamines and prostaglandin release. There is substantial evidence that prostaglandins are synthesized and released in response to endogenous or exogenous NE in the eye.\(^6\) Prostaglandins of the E series modify sympathetic neurotransmission by blocking NE release from nerve terminals and by inhibiting NE action at the effector cell membrane.\(^7\) This inhibitory effect provides a possible explanation for the diminishing hypotensive response to repeated NE administration. It is noteworthy that Langham and Palewicz\(^5\) did not observe a diminished hypotensive response after repeated administrations of NE 4%. This may be related to the stronger concentration they used.

Another possible mechanism of adaptation is related to the elevation of IOP observed soon after NE treatment. We observed this early rise in IOP in six rabbits treated with NE alone, but the early time course was not monitored in the animals.
treated with NE and flurbiprofen. It is possible that the early rise of IOP may diminish or postpone the later hypotensive response, resulting in the appearance of adaptation to NE. In our experiments the IOP did not usually drop from the 5 to the 7 hr reading, indicating that the maximal hypotension occurred before 7 hr. Therefore a direct relationship may exist between the degree of early IOP rise and the subsequent diminishing IOP fall.

Waitzman et al.6 blocked the hypertensive response to NE with indomethacin. After sympathectomy in rabbits, indomethacin prevented the ocular hyperemia that is associated with degeneration release of NE8 and also inhibited the enhanced outflow facility.9 These studies suggest that prostaglandins or other cyclooxygenase products mediate various actions of NE, including the IOP rise and subsequent adaptation of the IOP fall associated with repetitive NE administration.

Bhattacherjee and Hammond10 observed that indomethacin inhibited the ocular hypotensive effect of epinephrine in rabbits. However, the hypotensive effect of NE is probably not caused by cyclooxygenase products, since neither flurbiprofen in our study nor indomethacin6 blocked the hypotension.

Finally, other possible mechanisms for IOP modification include changes in the ocular penetration, neuronal uptake, or degradation of NE. However, cyclooxygenase products are not known to affect these processes. The IOP could also be modified by ocular inflammation mediated by prostaglandins. Nevertheless, suppression of the inflammation by a cyclooxygenase inhibitor would not establish a cause-effect relationship.

In summary, topical flurbiprofen was found to inhibit adrenergic adaptation to daily NE administration in the rabbit eye. The maximal effective concentration of flurbiprofen for this purpose is probably between 0.01% and 0.1%. Although not conclusive, our data strongly suggest that a cyclooxygenase product mediates this adaptation phenomenon. The mechanism may be related to postsynaptic inhibition of NE or to the early IOP hypertensive response.

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Key words: adrenergic adaptation, cyclooxygenase inhibitor, flurbiprofen, intraocular pressure, norepinephrine, prostaglandin, rabbit eye

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Langerhans cells in the normal conjunctiva and peripheral cornea of selected species. Meryl M. Rodrigues, Geoffrey Bowden, Joseph Hackett, and Irene Bakos.

The distribution of Langerhans cells (LCs) in human corneal and conjunctival epithelial sheets was investigated by histochemical, immunofluorescence, and immuno-electron microscopic methods. The LCs stained positive with ATPase and with antibodies to HLA-DR antigen and were negative to DOPA-oxidase. Human conjunctiva showed 250 to 300 LCs/ mm² compared to 15 to 20/mm² in the peripheral third of the corneal epithelium; approximately similar numbers of LCs were present...