expect that the competition for $\alpha_2$ receptor occupancy by the simultaneous addition of clonidine would eliminate this effect and demonstrate a final contraction of the dilator that was equal to or less than that obtained by phenylephrine alone. In fact, the addition of clonidine did not alter the NPY-enhanced phenylephrine-induced contraction of the dilator, thus making it unlikely that NPY functions as an $\alpha_2$-adrenergic receptor antagonist in our system.

Further experiments clearly are needed to define the mechanism by which NPY acts on the iris dilator muscle. A post-junction receptor, perhaps NPY-specific, may well mediate its effects. While NPY does not seem to act on the $\alpha_2$-adrenergic receptor, our data do not exclude the possibility of a different presynaptic receptor mechanism to facilitate norpinephrine release.

**Key words:** neuropeptide Y, iris dilator, muscle contraction, phenylephrine, adrenergic nervous system

References

effect in the vitreous. PGE levels, higher in placebo-treated aphakic eyes than in phakic ones, were elevated further by epinephrine treatment (from 388.40 to 1851.60 pg/ml in aqueous of aphakic eyes, and from 236.40 to 850.60 pg/ml in vitreous also of aphakic eyes). Our findings relate to the pathogenesis of epinephrine-induced maculopathy and to the mechanism of the ocular hypotensive effect of epinephrine. Invest Ophthalmol Vis Sci 29:332–334, 1988

The mechanism by which topically applied epinephrine reduces intraocular pressure remains unclear, as does the pathogenesis of epinephrine-induced macular edema. The apparent induction of prostaglandin synthesis by adrenergic agents seems relevant, but, to our knowledge, only one investigation has dealt with induction of prostaglandins by topical epinephrine in vivo.1

We wished to determine whether topically applied epinephrine could induce detectable amounts of prostaglandin E (PGE) in intraocular fluids in vivo, and whether aphakia influenced the accumulation of ocular PGE.

Materials and Methods. Pigmented Dutch Strain male rabbits (1.5–2.5 kg) were examined by slit-lamp and indirect ophthalmoscopy; they were treated according to the ARVO Resolution on the Use of Animals in Research. Those showing signs of conditions associated with prostaglandin biosynthesis were excluded. They were divided into six groups in a double-masked fashion and given 1.25% epinephrine eye drops (Epista Senju Co., Osaka, Japan) three times daily, 0.5% indomethacin eye drops (Epista Senju Co.) three times daily, or placebos. Regimens were as follows: Group 1, epinephrine and indomethacin; Group 2, epinephrine and indomethacin placebo; Group 3, epinephrine placebo and indomethacin; Group 4, placebo only. Animals in Group 5 (given epinephrine and placebo) and Group 6 (placebos only) underwent intracapsular lens extraction 1 month before experimental treatments began. All treatments continued for 5 months.

Animals were anesthetized with sodium pentobarbital (0.6 mg/kg, i.v.); eyeballs were rapidly enucleated and immediately frozen in liquid nitrogen, then stored at −11°C until PGE assay. The aqueous humor and the vitreous body were isolated, and prostaglandins were extracted using a modified method according to Collins and Hennan. The vitreous body was homogenized in a blender and centrifuged (10,000 g, 2°C, 20 min). Phosphate buffer (1 M at pH 7.4) was added to the aqueous humor or the vitreous body supernatant. The solution was acidified to pH 3 with HCl, and prostaglandins were extracted with diethyl ether. After centrifugation (2,000 g, 10 min), the ether layer was collected and dried under a gentle stream of nitrogen at room temperature. The residue was dissolved in assay buffer. Levels of PGE were determined by radioimmunoassay using the PGE (125I) RIA kit (available from E.I. du Pont de Nemours and Co., New England Nuclear Products, Boston, MA).

Statistical analyses used were Bartlett’s test and Mann-Whitney method.

Results. In the aqueous humor (Fig. 1), the level of PGE was lower (P < 0.05) in Group 1 than in Group 2, indicating that topically applied indomethacin inhibits epinephrine-induced biosynthesis of PGE in the aqueous. The level was higher (P < 0.05) in aphakie eyes than in identically treated phakic ones, and was higher in Group 5 (epinephrine-treated) than in Group 6 (receiving no epinephrine) (P < 0.05). The average level in Group 5 differed from the average level in Group 6 by 1463 pg/ml; the difference between Groups 2 and 4 was 242 pg/ml.

Vitreal levels of PGE (Fig. 2) were higher in Groups 1 and 2 (epinephrine) than in Groups 3 and 4 (no epinephrine) (P < 0.01, P < 0.05), but were essentially unaffect ed by indomethacin (comparing Groups 1 and 2 or comparing Groups 3 and 4). Vitreal levels of PGE were higher in aphakic than in identically treated phakic eyes (P < 0.01), and were higher in Group 6 than in Group 4 (P < 0.05). The average PGE level was 118 pg/ml higher in Group 2 than in Group 4, and was 614 pg/ml higher in Group 5 than in Group 6.

Discussion. Prostaglandin, once believed to increase intraocular pressure,2 has now been shown to reduce it.3 The present study supports evidence1,4,5 that topical epinephrine reduces intraocular pressure by inducing prostaglandin synthesis. The mean quantity of epinephrine-induced PGE in the aqueous of phakic eyes (407 pg/ml) certainly seems sufficient to effect biological action. However, the results were obtained from a study with substantially excessive...
Fig. 2. Concentrations of PGE in the vitreous humor of rabbit eyes treated with epinephrine (epi) and/or indomethacin (indo), or with placebo (pla) alone for 5 months. Values are mean ± SEM.

doses of epinephrine and also used rabbits. These factors indicate that the results may not be directly comparable to the clinical situation.

We do not support the suggestion 6 that so-called epinephrine-induced cystoid macular edema (CME) of aphakic eyes results from increased retinal uptake of topical epinephrine. Topical epinephrine causes disruption of the blood-aqueous barrier in phakic humans,7 and disruption of the blood-aqueous and the blood-retinal barriers in rabbits8 (though not necessarily in phakic monkeys).7 Topical indomethacin inhibits these actions,8 indicating that disruption of the blood-ocular barrier is at least partially mediated by cyclooxygenase products. (It is possible, however, that epinephrine is indeed the pathologic agent and is inhibited when indomethacin blocks Ca2+.) Lens extraction itself naturally stimulates prostaglandin production.9 In the present study, the effects of epinephrine on prostaglandin production between phakic and aphakic groups were compared, and it was found that epinephrine more effectively stimulates or actually more effectively accumulates prostaglandin production in aphakic eyes than in phakic eyes.

We propose that prostaglandins or other cyclo-oxygenase products may induce breakdown of the blood-ocular barrier, resulting in aphakic CME or in epinephrine maculopathy (similar conditions that are often confused). Prostaglandins, synthesized in the anterior uvea in response to topical epinephrine and/or surgical trauma, may accumulate when active prostaglandin transport10 has been disturbed by surgery. Indomethacin failed to influence PGE levels in the vitreous of phakic eyes, suggesting that intact transport mechanisms10 influence PGE levels more than indomethacin does (possibly, however, indomethacin simply did not penetrate to the vitreous.)

Our suggestions will receive further support, as will clinical use of indomethacin to prevent aphakic CME,9 if indomethacin is found to inhibit epinephrine-induced PGE synthesis in aphakia. Studies along this line are in progress.

Key words: prostaglandin E synthesis, epinephrine, radioimmunoassay, aqueous and vitreous, indomethacin

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