EP3, But Not EP2, FP, or TP Prostanoid-Receptor Stimulation May Reduce Intraocular Pressure

L. David Waterbury,* Richard M. Eglen,* George F. Faurot,* and Gary F. Cooper†

Stimulation of DP, but not TP or FP, prostanoid receptors has previously been shown to reduce intraocular pressure (IOP) in rabbits. However the role of EP receptors (EP1, EP2, and EP3 subtypes) has not been studied extensively. Sulprostone, RS-61565, and RS-20216 have been studied for effects on rabbit IOP, and their prostanoid-receptor profiles characterized. The data suggest that the EP3, but not EP2, FP, or TP activity of these agonists correlated with the intraocular hypotensive effects. Moreover, RS-20216 lowered IOP at a dose of 5 μg for up to 12 hr after administration. In contrast to PGE1 and PGE2, which elicited both hyper- and hypotensive responses, sulprostone, RS-61565, and RS-20216 elicited only a hypotensive responses with no signs of ocular irritation. Thus stimulation of the EP3 receptor results in a lowering of IOP in rabbits. Compounds specific for this receptor subtype may act as novel therapeutic agents for the treatment of glaucoma. Invest Ophthalmol Vis Sci 31:2560-2567, 1990

It has been proposed1 that distinct receptor types exist for each of the naturally occurring prostaglandins as summarized in Table 1. The role of each of these subtypes in lowering intraocular pressure (IOP) has not been characterized extensively. Several naturally occurring prostaglandins lower IOP in rabbits, cats,2-3 primates,6,7 and humans.8 Both prostaglandin E1 (PGE1) and PGE2 raise and lower rabbit IOP,2 which may suggest an interaction at more than a single receptor subtype. The effects of PGE2α and its analogues on lowering IOP were shown in rabbits9 to correlate inversely with their efficacy at FP receptors. The selective FP agonist, fluprostenol, did not lower IOP, suggesting that the ocular hypotensive effect of PGE2α was not mediated by an FP receptor.9 Both PGD2 and the selective DP agonist, BW 245C, lowered IOP in rabbits, suggesting that DP receptor agonism was also associated with IOP lowering.10,11 The selective and potent IP agonist, iloprost, decreases IOP in rabbits and dogs,12 although this effect has not been reported in primates.13 U-46619 is a potent and selective TP agonist14,15 previously shown14 to cause a slight but statistically significant increase in IOP in rabbits. However, other studies show no effect of the TP receptor agonist, U44069, in cats.2 Taken together, these data suggest that DP, but not FP or TP receptors, mediate IOP reduction.

A problem with using naturally occurring prostanoids to characterize the receptors responsible for IOP lowering is their lack of prostanoid-receptor selectivity.1 The role of EP receptor subtypes (EP1, EP2, or EP3), in particular, in the ocular hypotensive response to PGE1 or PGE2 has not been characterized. Consequently, our attention focused on the IOP-lowering effects of several synthetic prostaglandins. These compounds might be more selective for a particular EP receptor subtype, thereby avoiding the systemic and ocular side effects associated with the naturally occurring prostaglandins.16,17

We investigated two synthetic standards (sulprostone and U-46619) and two structural analogues of PGE2 (RS-61565 and RS-20216) to determine the possible relationship of IOP-lowering activity with prostanoid-receptor stimulation. RS-61565 and RS-20216 act as potent EP3 receptor agonists. The former also exhibits significant TP and to a lesser extent FP receptor agonism. For direct comparisons to be made, the effects of PGE1 and PGE2 on IOP were also studied. The structures of these compounds are shown in Figures 1 and 2.

Sulprostone is a potent EP3 receptor agonist which has been shown to exert abortifacient effects,18 although its effects on IOP are unknown. Enprostil is also a potent and selective EP3 agonist, but at higher concentrations it has FP and TP agonist properties.19 RS-61565-007 (R-allene isomer) and the racemic RS-20216 (Fig. 2) are related structurally to enprostil and sulprostone, respectively, but their prostanoid-
Table 1. Classification of prostanoid receptors (after Coleman et al, 1985)

<table>
<thead>
<tr>
<th>Receptor</th>
<th>Natural prostaglandin</th>
<th>Synthetic agonist</th>
<th>Synthetic antagonist</th>
</tr>
</thead>
<tbody>
<tr>
<td>DP</td>
<td>PGD₂</td>
<td>BW 245C</td>
<td>BW A868C</td>
</tr>
<tr>
<td>EP**</td>
<td>PGE₁/PGE₂</td>
<td>Sulprostone</td>
<td>AH 6809/SC-19920</td>
</tr>
<tr>
<td>FP</td>
<td>PGF₂a</td>
<td>Fluprostenol</td>
<td>NA</td>
</tr>
<tr>
<td>IP</td>
<td>PGI₁</td>
<td>Iloprost</td>
<td>NA</td>
</tr>
<tr>
<td>TP</td>
<td>TXA₂</td>
<td>U 46619</td>
<td>BM 13.177</td>
</tr>
</tbody>
</table>

* EP receptors form three subtypes, denoted as EP₁, EP₂, and EP₃. These are characterized as shown below:

| EP₁      | PGE₁/PGE₂             | Sulprostone       | AH 6809/SC-19920   |
| EP₂      | PGE₁/PGE₂             | Butaprost         | NA                 |
| EP₃      | PGE₁/PGE₂             | Sulprostone/enprostil | NA             |

NA, not available.

receptor profiles have not been previously reported. We compared the effect of each of these synthetic prostaglandins on rabbit IOP with its prostanoid receptor-agonist profile determined in vitro. Preliminary accounts of these data were presented elsewhere in abstract form.²⁰,²¹

Materials and Methods

Prostanoid-Receptor Studies

Prostanoid-receptor profiles of the synthetic prostaglandins were characterized in vitro using methods previously described (Table 2). All tissues were isolated from Dunkin-Hartley guinea pigs (male, 250–400 g) with the exception of the colon which was isolated from Sprague-Dawley rats (male, 200–250 g). All animals were killed by CO₂ asphyxiation before tissue isolation. All animals were treated according to the ARVO Resolution on the Use of Animals in Research.

All tissues were isolated and transferred to warm (37°C), physiologic salt solution (PSS; pH 7.4) containing 1 μM indomethacin. Guinea-pig ileum and rat colon were gently flushed intraluminally and suspended under 1.0-g tension in Tyrode PSS. Guinea-pig trachea, previously cut into zigzag strips and rings of guinea-pig thoracic aorta were suspended under 1.0-g tension in Krebs PSS. Guinea-pig vas deferens were suspended between parallel platinum electrodes in Krebs PSS, under 0.5-g tension. All preparations were allowed 60 min to equilibrate. They were then exposed to KCl (50 mM), with the exception of vas deferens, for 5 min. The tissues were then washed and allowed to regain baseline tension. Phenoxybenzamine and atropine (1 μM) were added to each preparation, with the exception of the trachea and vas deferens, for the rest of the study.

Contractile responses were determined in guinea-pig ileum (EP₁), rat colon (FP), and guinea-pig aorta (TP). Since the guinea-pig trachea and rat colon also possess EP₁ and TP receptors, AH 6809 (3 μM) and BM 13.177 (3 μM) were added to inhibit stimulation of these receptors, respectively. The EP₂ receptors mediate relaxation of a precontracted (10 μM carbachol) guinea-pig trachea, and the EP₃ receptors inhibit "twitch" responses of the field-stimulated (supramaximal voltage, 5 Hz; duration, 1-msec; trains of stimulation at 2-min intervals) guinea pig vas deferens.

All compounds were added on a cumulative basis using incremental concentrations spaced at 0.5 log intervals. Only one agonist was applied to each tissue with the responses being normalized against the maximum response elicited by a full prostanoid agonist, ie, EP₁-PGE₂, EP₂-PGE₂, EP₃-sulprostone, FP-PGF₂α, and TP-U46619. All responses were determined as changes in isometric tension (mg). These responses were used to derive the potency, calculated as the EC₅₀, using nonlinear iterative curve-fitting procedures.

IOP Studies

These studies were conducted using young New Zealand albino rabbits (female, 2.0–3.0 kg). The rabbits had not previously received topical drugs of any kind. The IOP was measured with a pneumotonometer (Digilab, Bio-Rad, Cambridge, MA) calibrated at the beginning and end of each study by a Digilab calibrator equipped with a membrane sensor. Before the studies, the rabbits were acclimated to study conditions by removing them from their cages and taking unrecorded measurements after topical administration of the corneal anesthetic proparacaine HCl (Allergan, Irvine, CA). The rabbits were then randomly assigned into treatment groups of seven animals each. During initial tonometry readings, rabbits with more than a 3-mm Hg IOP difference between eyes were excluded. The basal IOP of the animals we used ranged from 19–25 mm Hg.
Compounds were administered (50-μl volume) to one eye, and an equivalent volume of vehicle was administered to the contralateral eye, which acted as a control. An additional group of animals received vehicle in both eyes. All doses of prostaglandins are given in μg/eye. Prostaglandin-induced IOP effects were compared with both IOP effects in vehicle-treated rabbits and in animals in which vehicle was administered to the contralateral eye. This second parameter allowed assessment of the potential systemic effects. All experiments were blinded. The IOP measurements were made 1 min before drug administration and at intervals 0.5–6 hr thereafter. In experiments in which only RS-20216 was tested, additional measurements were also made up to 24 hr after administration.

In all studies ocular irritation (defined by lid closure and hyperemia) were recorded. The protein content in the aqueous humor was not determined. Dose-response curves were constructed with each synthetic compound. However, dose-response curves were not constructed with PGE₁ and PGE₂, which acted as irritants, or with U-46619 which was lethal at doses of 25 μg and above.

In studies with U-46619 only, the effect of TP antagonism was studied. The TP receptor antagonist BM 13.177 (5 μg) was administered in separate experiments 30 min before administration of U46619. BM 13.177 was shown, in preliminary experiments, to exert no effect on IOP when given alone.

To determine the concentration of sulprostone in the eye after dosing, ³H-sulprostone was used. This procedure was undertaken to relate the concentration of sulprostone in the aqueous humor with the potency of this agonist at prostanoid receptors. Radiolabeled derivatives of the other compounds were either unavailable or not studied. A solution containing 0.5 μg of unlabeled sulprostone and 1 μCi of ³H-sulprostone was applied (50 μl) to both eyes of four rabbits. Sixty minutes later the rabbits were killed with an overdose of sodium pentobarbital and their eyes thoroughly rinsed in situ with 0.154 mM NaCl. Samples (100–300 μl) of aqueous humor were then obtained with a 28-gauge needle attached to a syringe. The radioactivity of each aliquot was determined using liquid scintillation spectrometry (Packard model 1900CA, Downers Grove, IL). The radioactivity content in each sample was compared with the dosing solution (1 nmol = 101,802 dpm) to estimate the molar concentration of sulprostone in aqueous humor.

**Statistical Analysis**

*In vitro studies:* Statistically significant differences were assessed by unpaired student t-tests with \( P < 0.05 \) considered significant.

*In vivo studies:* Analysis of variance was done to test for significant effects of treatment. At each time paired data were compared between the IOP effect in compound-treated eyes and vehicle-treated contralateral eyes. In addition, the IOP of vehicle-treated eyes of the control group were also compared with the treated eyes. All statistics were analyzed using general linear models (SAS Institute, Cary, NC).
Compounds used: These were RS-61565 (methyl-(4,5,6R)-7-[(IR,2R,3R)-3-methyl-2-{(E)-(3R)-3-hydroxy-4-phenoxy-1-butenyl]-5-oxocyclopentyl]-4,5-heptadienoate; Syntex, Palo Alto, CA); RS-20216 [(±)-7-{([1R*,2R*,3R*)-3-hydroxy-2-{(E)-(3R*)-(3-hydroxy-4-phenoxy-1-butenyl)]-5-oxocyclopentyl)-N-(methylsulfonyl)-4,5-heptadienamide; Syntex); sulprostone, (Pfizer, New York, NY); [3H]-sulprostone (96 Ci/mmol; Syntex); PGE₁ (Ono, Osaka, Japan); PGE₂ (Cayman, Ann Arbor, MI); and U-46619 (9,11 methanoepoxy PGH₂; Cayman). All compounds were dissolved in ethanol. For in vitro studies the stock concentration was usually 32 mM. For in vivo studies, the stock solution was 1% ethanol (w/v), and vehicle solutions consisted of 1% ethanol in water.

Results
Prostanoid-Receptor Studies
The potencies (−log of values of the effective concentration for 50% of animals [EC₅₀]) of a range of standard prostanoids at receptors in isolated tissues are shown in Table 3. These data were reported previously.¹⁹ Each naturally occurring prostanoid had activity at several receptors, but they were most potent at a single site. The order of selectivity was as follows:

- PGE₁ - EP₃ > EP₁ > EP₂ > FP > TP
- PGF₂α - FP > EP₁ = TP = EP₃ > EP₂
- U46619 - TP > EP₁ = EP₂ = EP₃ = FP
- PGI₂ - EP₁ > EP₃ > EP₂ > FP > TP

The potencies (−log EC₅₀ values) of the synthetic compounds at these receptors are shown in Table 4. RS-61565, sulprostone, and RS-20216 acted as highly potent EP₁ receptor agonists. These agonists had little or no EP₂ activity. Due to enhancement of ileal spontaneous activity, EP₁ activity could not be determined accurately. RS-61565 and RS-20216 had FP activity at concentrations approximately 100-fold greater than those which stimulated EP₁ receptors. Sulprostone was more selective than either RS-61565 or RS-20216. Moreover, sulprostone did not have TP activity, and RS-61565 had similar potencies at the EP₁ and TP receptors. RS-20216 was approximately 500-fold more selective for EP₁ in comparison with the TP receptor. The order of selectivity was as follows:

RS-61565 - EP₁ = TP > FP > EP₂

See refs. 14, 15, and 19 for references and reviews.
Table 3. Potencies (−log EC₅₀) of standard prostaglandins at receptors in various tissues

<table>
<thead>
<tr>
<th>Prostanoid receptor subtype</th>
<th>EP₁ (ileum)</th>
<th>EP₂ (trachea)</th>
<th>EP₃ (vess deferens)</th>
<th>FP (colon)</th>
<th>TP (aorta)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PGE₁</td>
<td>7.81 ± 0.08</td>
<td>6.57 ± 0.06</td>
<td>8.46 ± 0.11</td>
<td>6.23 ± 0.07</td>
<td>NR</td>
</tr>
<tr>
<td>PGE₂</td>
<td>6.84 ± 0.12</td>
<td>7.43 ± 0.09</td>
<td>7.70 ± 0.06</td>
<td>7.21 ± 0.12</td>
<td>&lt;5.0</td>
</tr>
<tr>
<td>PGF₂α</td>
<td>6.21 ± 0.05</td>
<td>NR</td>
<td>6.16 ± 0.06</td>
<td>8.02 ± 0.09</td>
<td>6.20 ± 0.03</td>
</tr>
<tr>
<td>U-46619</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>7.44 ± 0.12</td>
</tr>
</tbody>
</table>

Values are −log EC₅₀ ± SE mean, n = 4-8; NR, no response (1 nM-30 µM).

Table 4. Potencies (−log EC₅₀) of synthetic prostaglandins at receptors in various tissues

<table>
<thead>
<tr>
<th>Prostanoid receptor subtype</th>
<th>EP₁</th>
<th>EP₂</th>
<th>EP₃</th>
<th>FP</th>
<th>TP</th>
</tr>
</thead>
<tbody>
<tr>
<td>RS-61565</td>
<td>NR*</td>
<td>NR</td>
<td>8.51 ± 0.14</td>
<td>6.41 ± 0.06</td>
<td>8.48 ± 0.06</td>
</tr>
<tr>
<td>Sulprostone</td>
<td>NR*</td>
<td>NR</td>
<td>5.84 ± 0.05</td>
<td>9.32 ± 0.07</td>
<td>5.21 ± 0.11</td>
</tr>
<tr>
<td>RS-20216</td>
<td>NR*</td>
<td>NR</td>
<td>8.56 ± 0.08</td>
<td>6.85 ± 0.13</td>
<td>6.00 ± 0.07</td>
</tr>
</tbody>
</table>

Values are mean ± SE mean, n = 4-8; NR, no response.

* An increase in spontaneous activity was observed which persisted after washout. The variability of this response was impossible to quantify and no −log EC₅₀ value was calculated.
and 5 μg) studied also showed significant lowering up to 8 hr after administration. The lowest dose of RS-20216 (0.005 μg) studied was inactive (Fig. 7). The maximum lowering effects of the two highest doses (0.5 μg and 5 μg) were observed 4 hr after administration (Table 5). The highest dose studied (5 μg) elicited a prolonged IOP lowering that was significant at 8 hr, but not at 24 hr, after administration. At this dose, a contralateral effect was not observed (Fig. 8).

**Discussion**

Prostaglandins have been previously shown to reduce IOP, although the receptor subtype by which these effects are mediated remains to be defined. Such studies have been hampered previously both by the lack of use of a coherent prostanoid-receptor classification and the lack of potent and selective receptor ligands. One scheme (Coleman et al.) provides a rational framework for nomenclature of prostanoid receptors, and we adopted this in the present study.

The role of prostanoid receptors in the control of IOP has not been studied intensively to our knowledge. FP receptor stimulation does not reduce IOP, and TP stimulation either has no effect or results in a marginal reduction in IOP. DP stimulation probably has a hypotensive effect, and the effects of EP receptor stimulation are presently unknown.

The effects of topically administered PGE_1 and PGE_2 are biphasic; both increases and decreases in IOP have been reported. Prostaglandin PGE_2 (1 μg) has also been shown to lower IOP in rabbits. However, the prostanoid-receptor profile of PGE_2 has yet to be reported. Since PGE_1 and PGE_2 can stimulate EP_1, EP_2, and EP_3 receptors, the role of these subtypes in reducing IOP are unknown. To circumvent some of these problems, stable synthetic PGE_2 analogues were studied for effects on IOP. These compounds may be selective for a particular prostanoid subtype and allow a more definitive characterization to be made.

In isolated tissues, PGE_1 and PGE_2 acted as agonists at EP_1, EP_2, EP_3, and FP receptors. Of the compounds studied, only these prostanoids showed both a hypertensive and hypotensive effect on IOP. It is unlikely that these effects were mediated by FP receptors, since the selective FP agonist, fluprostenol, was inactive at reducing IOP. Stimulation of EP receptors probably mediated these effects of PGE_1 or PGE_2 on IOP. It should be noted that PGE_2 has also been reported to lower rabbit IOP. However, as we showed, PGE_2 can stimulate EP_1, EP_3, and TP receptors (at higher concentrations than those which stimulate FP receptors).

U46619 was shown in vitro to act as a selective TP agonist, in agreement with the literature. Little meaningful reduction and no increase in IOP was observed. Similar findings have been reported previously in rabbits and cats. Moreover, the lack of the effect of TP receptor antagonist, BM 13.177, on the small IOP reduction induced by U46619, further suggested an absence of TP receptor-mediated stimulation on the IOP responses. Taken together, these data suggest that the TP receptor is not involved in the reduction of IOP in rabbits.

These data suggest that either stimulation of EP_1, EP_2, or EP_3 but not TP or FP receptors can lower IOP in rabbits. Sulprostone is a potent EP_3 agonist, but lacks EP_2, FP, and TP agonism. It was hypothesized that this would act as a useful probe to study the role of EP receptors in the IOP response. In contrast to PGE_1 or PGE_2, with sulprostone only a profound and lasting hypotensive effect was seen. The reason for the hypertensive effect seen with PGE_1 and PGE_2 but not with sulprostone is unknown. Since sulprostone, in contrast to PGE_1 or PGE_2, lacks EP_2 agonism; it is...
Table 5. Effect of topically administered prostaglandins on rabbit IOP

<table>
<thead>
<tr>
<th>Prostanoid</th>
<th>Dose μg/50 μl</th>
<th>Time of maximum effect</th>
<th>IOP (mm Hg ± SEM)</th>
<th>Change*</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Initial</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vehicle RS-61565</td>
<td>0.00</td>
<td>2 hr</td>
<td>20.1 ± 0.4</td>
<td>-0.6 ± 1.2</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>0.10</td>
<td>2 hr</td>
<td>21.0 ± 0.6</td>
<td>-7.9 ± 0.6†</td>
<td>4 hr</td>
</tr>
<tr>
<td></td>
<td>0.25</td>
<td>2 hr</td>
<td>24.0 ± 0.4</td>
<td>-7.4 ± 1.0†</td>
<td>4 hr</td>
</tr>
<tr>
<td></td>
<td>2.50</td>
<td>2 hr</td>
<td>25.1 ± 0.4</td>
<td>-6.4 ± 0.9†</td>
<td>4 hr</td>
</tr>
<tr>
<td>Vehicle U-46619</td>
<td>0.00</td>
<td>2 hr</td>
<td>19.9 ± 0.4</td>
<td>-0.5 ± 0.5</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>0.05</td>
<td>2 hr</td>
<td>20.6 ± 0.5</td>
<td>-2.4 ± 0.6§</td>
<td>2 hr</td>
</tr>
<tr>
<td>Vehicle sulprostone</td>
<td>0.00</td>
<td>2 hr</td>
<td>22.9 ± 0.5§</td>
<td>-0.3 ± 0.4</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>0.50</td>
<td>2 hr</td>
<td>22.9 ± 0.5</td>
<td>-6.0 ± 0.6†</td>
<td>&lt;6 hr</td>
</tr>
<tr>
<td></td>
<td>5.00</td>
<td>2 hr</td>
<td>21.3 ± 0.7</td>
<td>-5.8 ± 1.2†</td>
<td>&lt;6 hr</td>
</tr>
<tr>
<td>Vehicle RS-20216</td>
<td>0.00</td>
<td>2 hr</td>
<td>18.8 ± 0.6§</td>
<td>-1.2 ± 0.9</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>0.05</td>
<td>2 hr</td>
<td>18.6 ± 0.4</td>
<td>-3.9 ± 0.7†</td>
<td>&gt;4 hr</td>
</tr>
<tr>
<td></td>
<td>0.50</td>
<td>4 hr</td>
<td>20.1 ± 0.6</td>
<td>-4.3 ± 1.0†</td>
<td>&gt;8 hr</td>
</tr>
<tr>
<td></td>
<td>5.00</td>
<td>4 hr</td>
<td>20.4 ± 0.4</td>
<td>-8.2 ± 0.6†</td>
<td>12 hr</td>
</tr>
</tbody>
</table>

* Negative signs indicate a reduction in IOP.
† P < 0.01 vs. vehicle control for dose shown above (each experiment had own separate control groups).
§ Control mean of three separate experiments.
¶ Control mean of four separate experiments.

It is possible that the hypertensive effect of PGE₁ and PGE₂ were mediated by this subtype. Further experiments using the selective EP₂ agonist, butaprost, are required to substantiate this hypothesis. It was concluded that EP₂ receptors do not reduce IOP. Since sulprostone also lacks FP and TP agonism, these data agree with our studies and suggest that FP and TP are not involved in IOP reduction.

RS-61565 is an analogue of the EP₃ agonist, enprostil. However, in contrast to enprostil, RS-61565 showed no selectivity between EP₃ and TP receptors. This agonist caused a similar IOP reduction to that observed with sulprostone, but it was greater than that observed with PGE₁ or PGE₂. This compound probably acted by stimulation of EP₃ receptors to elicit the hypotensive response; although possessing potent TP agonist activity, our studies showed a lack of effect of TP and FP receptors in lowering IOP. At the doses studied, no dose dependency was seen. It is possible that these effects represent the maxima of the dose-response curve between 0.10-2.5 μg, with a threshold at 0.025 μg.

RS-20216 is a prostanoid that shares structural similarities with both sulprostone and RS-61565. The compound acted as a potent EP₃ receptor agonist, with minimal activity at the TP and FP receptors and, in this respect, resembled sulprostone. It also caused a profound and long-lasting IOP reduction. These data suggest a role for EP₃ agonism in IOP reduction. Recently it was shown that EP₂ receptors do not lower IOP, and our data agree with this. RS-20216, although somewhat less potent than sulprostone for EP₃ receptors, had a longer duration of action (8-12 hr) than sulprostone. The reason for the enhanced duration is unknown, but it suggests that the compound may have therapeutic utility. It should be noted that the potential abortifacient activity of compounds, such as sulprostone, may limit their usefulness if significant systemic absorption occurs.

In conclusion, these studies showed that FP, TP, and EP₂ receptors do not participate in IOP lowering in the rabbit. Selective stimulation of EP₃ receptors, however, may result in a profound and long-lasting...
decrease in IOP. Definitive evidence for the role of EP3 receptors in IOP lowering awaits the development of a selective EP3 antagonist. The design of compounds such as RS-20216 which are selective for the EP3 receptor may provide a novel approach to the design of therapeutic agents to reduce IOP.

Key words: prostaglandins, receptor subtype, intraocular pressure

References


