The intraocular pressure (IOP) lowering effects of prostaglandins and prostaglandin analogs

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SUMMARY
Prostaglandins (PG) are very effective ocular hyper- and hypotensive agents in the mammalian eye, with the direction and magnitude of the intraocular pressure (IOP) change varying by species, PG and dose. It is generally agreed that these drugs reduce intraocular pressure primarily by increasing uveoscleral outflow. They may also increase trabecular outflow facility though available evidence is less convincing. It has been hypothesized that PGs may increase facility of uveoscleral outflow in addition to their other mechanisms, but this has not yet been tested. Its potent ocular hypotensive action in primates, including man, Prostaglandin F2 alfa has received substantial study as a potential anti-glaucoma therapeutic agent, but the specific PG receptor(s) involved in all aspects of the response are unknown. In studying prostaglandin and prostaglandin analogs, there are a diverse variety of prostanoid receptor selective agonists. These included DP, EP (EP1, EP2 EP3), FP, IP and TP receptor selective compounds.

Key Words: Prostaglandins, uveoscleral outflow, trabecular outflow, intraocular pressure.

Prostaglandin-related agents are effective in decreasing intraocular pressure and have a low incidence of adverse drug reactions. Therefore these agents play an important role in the treatment of glaucoma (1). The primary and least ambiguous mechanism of action of PGs is an increase in uveoscleral outflow, which has been found across species in monkeys, rabbits and humans (2, 3).

The increase in uveoscleral outflow may result initially from relaxation of the ciliary muscle and later from biochemical restructuring of the components of its extracellular matrix (4).

The effect of naturally occurring PGs or their synthetic analogs on intraocular pressure appears to be receptor mediated. In the early 1980s, Coleman’s group (5) proposed a system of classification of PG and thromboxane (TX) receptors based on the responses of the smooth-muscle preparations to five prostanoids, PGD2, PGE2, PGF2α, PGJ2 and thromboxane A2. The nomenclature for receptors proposed by Coleman was P receptors, with a preceding letter indicating the natural prostanoid to which each receptor is most sensitive. Thus the receptors were termed DP, EP, FP, IP and TP, respectively (Table 1).

Table 1. Classification of prostanoid receptors after (Coleman et al, 1985)

<table>
<thead>
<tr>
<th>Receptor</th>
<th>Natural prosta glandin</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 A 886C</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>PGF2α</td>
<td>Fluprostanol</td>
<td>NA</td>
</tr>
<tr>
<td>IP</td>
<td>PGJ2</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, donated as EP1, EP2 and EP3. These are characterized as shown below

| EP1 | PGE1/PGE2 | Sulprostone | AH 6809/SC-19220 |
| EP2 | PGE1/PGE2 | Butaprost   | NA                |
| EP3 | PGE1/PGE2 | Sulprostone/enprostil | NA                |

NA: not available

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IOP reduction in dogs and monkeys is afforded by various receptor selective PG analogs implying the involvement of DP-, EP₁-, EP₂-, EP₃-, and FP receptors (6, 7). In humans, DP- and EP-receptor agonists appear to have a biphasic effect on IOP with an initial hypertension being the more pronounced response (8, 9). The use of natural prostaglandins (PG) such as PGD₂, PGE₂, PGF₂α, and PGI₂ for treating glaucoma is limited by their ocular side effects (7). Another problem with using naturally occurring prostanoids to characterize the receptors responsible for IOP lowering is their lack of prostanoid-receptor selectivity (10). 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.

The classification of prostaglandin analogs according to the binding affinities, potencies and selectivities as last proposed by Cayman (Table 2).

<table>
<thead>
<tr>
<th>Name</th>
<th>Receptor</th>
<th>Natural PG</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>15(R)-17-phenyltrinor prostaglandin F₂α isopropyl ester</td>
<td>FP</td>
<td>PGF₂α</td>
<td>There are no published reports of the intra ocular hypotensive properties</td>
</tr>
<tr>
<td>15(S) Latanoprost</td>
<td>FP</td>
<td>PGF₂α</td>
<td>There are no published reports of their biological activity and intra ocular hypotensive activity in particular of 15(S) Latanoprost.</td>
</tr>
<tr>
<td>15-keto Latanoprost</td>
<td>FP</td>
<td>PGF₂α</td>
<td>Although much less potent that the parent compound latanoprost, 15-keto latanoprost produces a small measure decrease (1mmHg) in the intra ocular pressure of normal cynomolgus monkeys at administrated at a dose of 1 mg/eye. Reduces IOP in glaucoma patients with few side effects.</td>
</tr>
<tr>
<td>Latanoprost (17-phenyl-13,14-dihydro PGF₂α)</td>
<td>FP</td>
<td>PGF₂α</td>
<td>Is a prodrug form.</td>
</tr>
<tr>
<td>Latanoprost (free acid)</td>
<td>FP</td>
<td>PGF₂α</td>
<td>Although it has been claimed that prostaglandin ethyl amides are not converted to the free acids in vivo, studies have shown that bovine and human corneal tissue converts it to the free acids.</td>
</tr>
<tr>
<td>Latanoprost ethyl amide</td>
<td>FP</td>
<td>PGF₂α</td>
<td>It would act very much like the free acid of latanoprost.</td>
</tr>
<tr>
<td>17-trifluoro metil phenyl 13-14 drydrotrinor prostaglandin F₂α</td>
<td>FP</td>
<td>PGF₂α</td>
<td>At a dose of 3mg/eye in the monkey, it was the most potent analog tested in reducing IOP, lowering the IOP 1-3 mmHg below the level achieved by latanoprost.</td>
</tr>
<tr>
<td>17-phenyltrinor prostaglandin F₂α isopropyl ester</td>
<td>FP</td>
<td>PGF₂α</td>
<td>It is a potential metabolite of Bimatoprost when administrated to intact animals. It produces a small but measurable decreases (1mmHg) in the IOP of normal cynomolgus monkeys when administrated at a dose of 1μg/eye2.</td>
</tr>
<tr>
<td>15-keto-17-phenyltrinor prostaglandin F₂α</td>
<td>FP</td>
<td>PGF₂α</td>
<td>Were recently introduced as alternative prostaglandin hypotensive prodrugs.</td>
</tr>
<tr>
<td>17-phenyltrinor prostaglandin F₂α amide (Lumigan) 9-keto fluosteranol isopropyl ester (metabolite) of Travoprost</td>
<td>FP</td>
<td>PGE₂</td>
<td>No studies on the pharmacology of this compound have been published.</td>
</tr>
<tr>
<td>15- (R)-17 phenyltrinor prostaglandin F₂α isopropyl ester</td>
<td>FP</td>
<td>PGF₂α</td>
<td>It is the Latanoprost-related isomer. There are no published report of the intraocular hypotensive properties of 15-17 phenyltrinor PGF₂α isopropyl ester.</td>
</tr>
<tr>
<td>Substance</td>
<td>Type</td>
<td>Notes</td>
<td>Reference</td>
</tr>
<tr>
<td>---------------------------------</td>
<td>--------</td>
<td>----------------------------------------------------------------------</td>
<td>-----------</td>
</tr>
<tr>
<td>Lumula</td>
<td>FP</td>
<td>Lumula is a hybrid eicosanoid analog, which incorporates the docosanoid features of unoprostone as well as the prostaglandin features of bimatoprost. Lumula is a good tool for testing the validity of the alternate mechanism theories. The compound is reported to retain ocular hypotensive properties but the nature of the receptors, which mediate, is disputed.</td>
<td></td>
</tr>
<tr>
<td>Prostaglandin F$_{2\alpha}$ alcohol</td>
<td>FP</td>
<td>Has ocular hypotensive activity</td>
<td></td>
</tr>
<tr>
<td>Prostaglandin F$_{2\alpha}$ alcohol methyl ether</td>
<td>FP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prostaglandin F$_{2\alpha}$ ethyl amide (Bimatoprost-Lumigan)</td>
<td>FP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prostaglandin F$_{2\alpha}$ isopropyl ester</td>
<td>FP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prostaglandin F$_{2\alpha}$ methyl ester</td>
<td>FP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unoprostone isopropyl ester (Rescula)</td>
<td>FP</td>
<td>Docosanoid its biological activities independent of any known prostaglandin receptors.</td>
<td></td>
</tr>
<tr>
<td>Iloprost</td>
<td>IP and EP$_1$</td>
<td>PGE$_2$, PGE$_1$ In whole animals, it acts as a vasodilator hypotensive, antidiuretic and prolongs bleeding time. Human treatment for idiopathic pulmonary hypertension. It has virtually no effect on human TP, IP, EP$_1$, EP$<em>2$, and FP receptors, it antagonizes the accumulation of cAMP in rabbit non-pigmented ciliary epithelial cells. The pharmacology of AL-8810 has not been published. It is effects on PGF$</em>{2\alpha}$ induced smooth muscle contraction It is a unique and novel pharmacological tool to help characterize FP receptor-mediated functions.</td>
<td></td>
</tr>
<tr>
<td>BW- A868C*</td>
<td>DP antagonist</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AL – 8810*</td>
<td>FP antagonist</td>
<td></td>
<td></td>
</tr>
<tr>
<td>THG 113*</td>
<td>FP antagonist</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AL 3138*</td>
<td>FP antagonist</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Antagonist of receptor

Woodward et al (11) did an experiment to investigate the pharmacological basis of PGF$_{2\alpha}$ induced ocular hypotension and examined the activity of prostanooid analogues with selectivity for individual receptor subtypes. They found that the highly selective FP receptor agonist fluoprostanol caused no meaningful IOP changes in monkeys, cats and rabbits. They investigated the possibility that PGF$_{2\alpha}$ altered IOP by stimulating a prostaglandin E$_2$ (EP$_1$, EP$_2$, EP$_3$) or a thromboxane A$_2$ (TP) sensitive receptor. They also reported that the EP$_2$ and EP$_3$ receptor subtypes may be involved in mediating PGF$_{2\alpha}$ induced ocular hypertension in cats and rabbits respectively, which is consistent with PGE$_2$, being a more potent ocular hypotensive than PGF$_{2\alpha}$ in these species. The prostanooid receptor responsible for PGF$_{2\alpha}$ induced effects on primate intraocular pressure remains, however to be identified.

Waterburry (12) investigated two synthetic standards (suprostone and U-46619) and two structural analogues of PGE$_2$ (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. For direct comparisons to be made, the effects of PGE, and PGE₂ on IOP were also studied. Compounds were administered (50-µl volume) to one eye, and equivalent volume of vehicle was administered to the contralateral eye in rabbits, which acted as a control. The IOP measurements were made one min before drug administration and at intervals 0.5-6 hr thereafter. Only RS-20216 was tested 24 hr after administration. The effects of topically administered PGE, and PGE₂ are biphasic; both increases and decreases in IOP [of what magnitude?] The doses of drugs are: RS-61565 (0.10 - 0.25 - 2.50 µg/50 µl), U-46619 (5 µg/50 µl), RS-20216 (0.05 - 0.50 - 5.00 µg/50 µl). In conclusion they found that EP₃, but not EP₂, FP or TP activity of these agonists correlated with the intraocular hypotensive effects. The stimulation of the EP₃ receptor resulted in a lowering of IOP in rabbits.

Toris (15) reported cats were treated twice daily for one week with PGA₂ (0.01%) to one eye and vehicle to the other. They found out PGA₂ significantly reduced IOP by a mean of at least 4-7 mmHg. Compared with contra lateral vehicle-treated control eyes, uveoscleral outflow in the treated eye was significantly increased by at least 50% using two different methods of measurement.

In Wang's (14) experiment the effect of prostaglandin (PG) F₂ alpha-isopropyl ester (IE), PGA₂, or PGA₂-IE on intraocular pressure (IOP) was tested in eight cynomolgus monkey eyes with argon laser-induced glaucoma. Dose-response testing and baseline IOP measurements were done. For multiple dose testing, 5 micrograms in 25 micro liters (0.02%) of each PG was topically applied twice daily for 5 days. The IOP was measured at 30- or 60-minute intervals for 6 hours after the morning dose each day. A significant reduction of IOP peaked at 5-9 mm Hg below baseline values on the 5th day of treatment for each PG. The ocular hypotensive effect of these PGs progressively became more pronounced during the course of twice daily dosing, with a significant reduction maintained at least 17 hours after some doses. These findings demonstrate that PGs other than F₂ alpha are potent ocular hypotensive agents in primates.

Serle (15) compared latanoprost (PhxA41) and isopropyl unoprostone (UF-021, Rescula) in normal and glaucomatous monkey eyes. This study was designed to compare the ocular hypotensive effects of latanoprost and unoprostone in cynomolgus monkeys with glaucoma and characterizes the prostanoid's mechanisms of action in normal cynomolgus monkey eyes. Intraocular pressure was measured daily at 0, 0.5, and 1 hour and hourly for 5 additional hours during 1 baseline day, 1 vehicle-treated day, and 5 days of therapy with either 0.005% latanoprost or 0.12% unoprostone applied twice daily, at 9:30 AM and 3:30 PM, to the glaucomatous eye of eight monkeys with unilateral laser-induced glaucoma. Intraocular pressure was significantly reduced after the first application for 4 hours with latanoprost and for 2 hours with unoprostone, up to 5.4 +/- 0.8 mm Hg (latanoprost) and 3.8 +/- 0.5 mm Hg (unoprostone). Intraocular pressure was significantly reduced for at least 18 hours following each PM dose of latanoprost. Intraocular pressure was not reduced 18 hours after each PM dose of unoprostone. An enhancement of the ocular hypotensive effect was observed from day 1 to day 5 with repeated dosing of either drug [what was the maximum reduction on the 5th day with each?]. Intraocular pressure was reduced 1 hour after the initial dose of either drug. Latanoprost produced a greater magnitude of IOP reduction for a longer duration of time than unoprostone after each application. Peak reductions and up to 27% with unoprostone. Despite the 20-fold greater concentration of unoprostone than latanoprost. Latanoprost appears to be more efficacious and potent than unoprostone in reducing IOP in glaucomatous monkey eyes drug altered outflow facility or aqueous humor flow rates. Latanoprost and unoprostone appear to reduce IOP in monkeys by enhancing uveoscleral outflow. Saito (17) and Aung (18) reported that when used as monotherapy latanoprost was more potent than unoprostone lowering IOP and that the combination of the two drugs enhanced IOP lowering effect only when latanoprost was added to unoprostone, but not when unoprostone was added to latanoprost. When latanoprost and unoprostone are used in combination, the IOP reduction did not exceed the IOP reduction obtained by latanoprost monotherapy.

Latanoprost has a high affinity for prostanoid receptor F (FP receptors) (19, 20). A study performed on monkey models reported an IOP reduction through FP receptors (19). Affinity of unoprostone for FP receptors is reported to be 800-fold lower than
that of Latanoprost (19, 20). However, it has been reported that unoprostone reduces IOP in rabbits and cats in which FP receptors are not related to IOP reduction (11, 21). Also in contrast to latanoprost, unoprostone shows a greater IOP lowering effect in rabbits or cats in which uveoscleral outflow accounts for a smaller portion of the total outflow (22, 23). These findings suggest that latanoprost and unoprostone reduce IOP through different hypotensive mechanisms.

Krauss (16) suggest that thromboxane-mimetics and EP\textsubscript{2}–agonists have opposing activities on contractile elements in the meshwork and may modulate trabecular outflow in a functionally antagonistic manner. Prostanoid effects on ciliary muscle appear rather modest compared to parasympathomimetic drugs. It is conceivable that TP-agonists may substantially affect trabecular outflow.

Crawford et al (24) examined the effects of two relatively selective PG agonists, SQ27896 (selective for the DP-receptor) and sulprostone (selective for EP\textsubscript{3} and EP\textsubscript{1} receptors) on IOP, pupil diameter and refraction in cynomolgus monkeys. SQ27896 in single or repetitive doses is clearly not an ocular hypotensive agent in normotensive cynomolgus monkeys. The absence of an IOP fall in these monkeys suggests that SQ27896 and presumably DP-receptor stimulation in general, do not substantially increase uveoscleral outflow in the monkey eyes.

Sulprostone lowerd IOP in these monkeys several mmHg after repeated treatment with some doses, the effect was inconsistent and not clearly dose dependent. The pupil response to sulprostone is similar to PGF\textsubscript{2α} but the slight changes in refractive error are the opposite from the effects generally observed after PGF\textsubscript{2α}. Although PGF\textsubscript{2α} may not be entirely selective for FP prostanoid receptors it is unlikely that either the refractive effects, or that much of the ocular hypotensive effect is mediated through EP\textsubscript{1} and EP\textsubscript{3} receptors.

Kelly (25) reported that, the ability of a number of prostaglandin F\textsubscript{2α} (PGF\textsubscript{2α}) analogs to mobilize intracellular Ca\textsuperscript{2+} [Ca\textsuperscript{2+}] and to compete for \[^3^H\]PGF\textsubscript{2α} binding to prostaglandin F\textsubscript{2α} receptors (FP) was evaluated. Radioligand binding studies measuring displacement of \[^3^H\] PGF\textsubscript{2α} by a variety of FP prostaglandin analogs yielded the following rank order of affinities: travoprost acid \([+\cdot]16\text{-m-trifluorophenoxy tetranor PGF}_{2\Delta}\text{; (+)-fluprostenol}] > bimatoprost acid (17-phenyl-trinor PGF\textsubscript{2α}) >> unoprostone (13, 14-dihydro-15-keto-20-ethyl PGF\textsubscript{2α}) = bimatoprost (17-phenyl-trinor PGF\textsubscript{2α} ethyl amide) ≥ Lumigan (bimatoprost ophthalmic solution). In FP functional studies, travoprost acid bimatoprost acid, unoprostone, bimatoprost and lumigan concentration dependently stimulated [Ca\textsuperscript{2+}] mobilization via the rat (A7r5 cells), mouse (3T3 cells), and cloned human ocular FP prostanoid receptors. The rank order of potency of these compounds at the FP receptor of the three species was similar and in good agreement with the determined binding affinities. The agonist effects of these compounds were concentration dependently blocked by the FP receptor-selective antagonist, AL-8810 (1β-fluoro-15-epi-15-indanyltetranor PGF\textsubscript{2α}) (K\textsubscript{i} = 0.5-1.3 μM). These studies have demonstrated that bimatoprost, unoprostone, and bimatoprost acid possess direct agonist activities at the rat, mouse, and human FP prostanoid receptor and that travoprost acid is the most potent of the synthetic FP prostaglandin analogs tested.

Fujino (26) reported that prostaglandin F\textsubscript{2α} receptors (FP) are G protein-coupled receptors that bind prostaglandin F\textsubscript{2α} (PGF\textsubscript{2α}), resulting in the activation of an inositol phosphate (IP) second messenger pathway. Alternative mRNA splicing generates two FP receptor isoforms. These isoforms, designated FP\textsubscript{A} and FP\textsubscript{B}, are otherwise identical except for their carboxyl termini. FP\textsubscript{B} is essentially a truncated version of FP\textsubscript{A} that lacks the 46 carboxyl-terminal amino acids, including four putative protein kinase C (PKC) phosphorylation sites. Until now, functional differences between these FP receptor isoforms have not been identified. It is reported that pretreatment with the PKC inhibitor bisindolylmaleimide I enhanced PGF\textsubscript{2α}–stimulated IP accumulation in transfected cells stably expressing the FP\textsubscript{A} isofom but not in cells stably expressing the FP\textsubscript{B} isoform. Whole-cell phosphorylation experiments showed a strong agonist-dependent phosphorylation of the FP\textsubscript{A} isoform but little or no phosphorylation of the FP\textsubscript{B}. Pretreatment of cells with bisindolylmaleimide I decreased PGF\textsubscript{2α}–stimulated phosphorylation of the FP\textsubscript{A} isoform consistent with a PKC-dependent phosphorylation. In vitro phosphorylation of an FP\textsubscript{A} carboxyl-terminal fusion protein by recombinant PKC\textsubscript{A} showed that the carboxyl terminus of the FP\textsubscript{A} is a substrate for PKC. These results suggest that PKC-dependent phosphorylation is responsible for differential regulation of second mes-
senger signaling by FP prostanoid receptor isoforms.

Woodward et al (27) reported that bimatoprost (lumigan) is pharmacologically unique and a highly efficacious ocular hypertensive agent. It appears to mimic the activity of a newly discovered family of fatty acid amides, termed prostanoids. Although it has been claimed to exert is biological actions without interacting with any known prostaglandin receptors, later it has shown that bimatoprost and its hydrolytic prodrug (bimatoprost acid) bind to do FP prostaglandin receptor (28).

A single dose of bimatoprost 0.03% reduced IOP in normal dogs to approximately 10 mmHg, with minimal post-dosing drift after 24 hr. In the laser induced ocular hypertensive monkey model of glaucoma, a single dose of bimatoprost 0.03% reduced IOP by approximately 35% at 6 hr post-treatment (27). Clinical studies have also demonstrated good 24-hr IOP control after single daily doses of bimatoprost 0.03% (29).

Latanoprost (13,14-dihydro-17 phenyl-18,19,20- trinor-PGF2α isopropyl ester is a prosta-glandin analogue developed for glaucoma treatment and is as equally effective as PGF2α on the FP/EP1 and EP3 receptors, but less potent on EP1 receptors. Interestingly, latanoprost exert very little effects on the EP2 receptor (30). Topical administration of latanoprost substantially reduces IOP in monkeys and in glaucoma patients (31).

9 beta-[3H] labeled latanoprost was studied in the cynomolgus monkey after intravenous, oral and topical administration. The plasma profile of radioactivity from HPLC separation of samples obtained after intravenous as well as topical administration on the eyes showed a rapid and complete hydrolysis of the ester. The pharmacologically active acid of latanoprost showed a maximum concentration 5 min post-topical administration and an elimination half-life of about 10 min. After oral administration no latanoprost and very little of its acid was present in plasma, indicating a first-pass metabolism resulting in more polar compounds. The tissue distribution after i.v. and topical administration was similar with organs of metabolism (liver) and elimination (kidney) containing the highest concentrations. After topical application much of the dose was found in the anterior ocular tissues but not in the posterior parts of the eye (32).

Latanoprost has been shown to reduce intraocu- lar pressure effectively in patients with open angle glaucoma and ocular hypertension during chronic therapy. Gondolfi (33) compared bimatoprost and latanoprost for efficacy and safety in patients with glaucoma or ocular hypertension. Both medications were effective and safe in IOP lowering throughout the study. The mean IOP was consistently lower with bimatoprost and patients in this group were significantly more likely than patients in the latanoprost group to achieve low target pressures throughout the day. Both study medications were well tolerated.

Susanna (34) reported that latanoprost and unoprostone have been shown to be effective in decreasing intraocular pressure when used alone or in combination with other ocular hypertensive agents. Both drugs, unoprostone and latanoprost are valuable for the treatment of different types of glaucoma. Latanoprost however has a more potent IOP lowering effect than unoprostone. All the available evidences show that these drugs produce a clinically significant additive ocular hypotensive effect when used in combination with any currently available a-adrenergic agonists, beta blockers, cholinergic agonists and local and systemic carbonic-anhydrase inhibitors.

**Cannabinoid Antagonists:** Both alpha and beta-adrenergic antagonists have been utilized in an attempt to discern the site of action of prostaglandin (PG) and tetra-hydrocannabinol (THC) in the eye. Both alpha- and beta-adrenergic antagonists (alpha-antagonists, phentolamine and phenoxybenzamine; beta-antagonists, propranolol and sotalol) caused a dose-dependent reduction in intraocular pressure and blood pressure and increased total outflow facility. The results are consistent with the concept that both alpha- and beta-adrenergic receptors are present in the anterior uvea and that vasomotor tone is essential to the maintenance of normal intraocular pressure. No antagonist reduced the PG-induced elevation of intraocular pressure unless the blood pressure was severely lowered. All antagonists inhibit the normal PG-induced increase in total outflow facility, indicating that these agents protect the blood-aqueous barrier from breakdown without altering the vasodilatory response to PG. All antagonists reduced the fall in intraocular pressure produced by THC by approximately 50 per cent, except for sotalol which completely abolished the intraocular pressure fall. Only the alpha-adrenergic antagonists prevented the THC-induced increase in total outflow facility. The
results indicate that true outflow facility may well be 
regulated exclusively by alpha-receptors. The data 
are consistent with the effect of THC being primarily 
a vasodilation of the efferent blood vessels of the 
anterior uvea. The partial inhibition by alpha-adrenegic 
agonists may also suggest a lesser role of 
THC on the afferent vessels.

Pate(36) reported that attempts to indirectly deter-
mine if a neuronal cannabinoid (CB1) receptor medi-
ates the intraocular pressure (IOP) reduction effects 
of arachidonoyl ethanolamide (AEA), its R alpha-
iso-propyl analog, and the non-classical cannabinoid, 
CP-55,940. A series of these cannabinoids were dis-
solved in an aqueous 10-20% 2-hydroxypropyl-beta-
cyclodextrin (2-HP-beta-CD) solution (containing 3% 
polyvinyl alcohol) and administered (25-62.5 
microliter) to normotensive rabbit eyes. This was 
repeated on animals pre-treated with a subcuta-
neous injection (2.5 mg/kg) of the highly specific CB1 
receptor antagonist, SR 141716A, dissolved in an 
aqueous 42% 2-HP-beta-CD solution. AEA, its R-
alpha-isopropyl analog and CP-55,940 reduced IOP 
upon topical application to a greater degree than was 
detected in the untreated eye. This reduction was 
eliminated for the latter two compounds by subcuta-
neous pretreatment of the rabbits with the CB1 recep-
tor antagonist, but the IOP properties of AEA 
remained unchanged. SR 141716A administered 
elevated the IOP of both eyes. A CB1 receptor 
seems involved in the IOP reduction induced by 
either R-alpha-isopropyl anandamide or CP-55,940. 
However, AEA apparently functions through a differ-
ent mechanism.

Lumigan represents a new generation IOP-lowering 
drugs, a highly efficacious and long-acting ocular 
hypotensive agent. It is reported (37) in the laser 
induced ocular hypertensive monkey model of glau-
coma a single dose of bimatoprost 0.03% reduced 
IOP by approximately 35% at 6 hr post-treatment. In 
a recent animal study (38) aqueous humor dynamics 
and IOP were studied in monkeys with unilateral 
laser-induced ocular hypertension before and after 
bilateral travoprost 0.004% administration treatment 
was twice daily for two days and on the morning of 
third day. In the hypertensive eyes on the treatment 
day versus baseline day, IOP was significantly 
reduced by 7.7 mmHg at 2.5 hours and by 9.1 mmHg 
at 16 hours after treatment. Travoprost increased 
uveoscleral outflow in the normotensive eyes, but not 
in the hypertensive eyes.

Travoprost produced a lower incidence of ocular 
irritation than PGF2α isopropyl ester at a dose of 1 
micron in the New Zealand albino (NZA) rabbit. 
Topical ocular application of travoprost produced a 
marked miotic effect in cats following doses of 0.01, 
0.03 and 0.1 micron. In the ocular hypertensive mon-
key, b.i.d. application of 0.1 and 0.3 micron of travo-
prost afforded peak reduction in intraocular pressure 
(IOP) of 22.7% and 28.6%, respectively. Topical 
application of travoprost was well tolerated in rabbits, 
cats and monkeys, causing no ocular irritation or dis-
comfort at doses up to 1 micron. Travoprost is a 
promising ocular hypotensive prostaglandin FP deri-
native that has the ocular hypotensive efficacy of 
PGF2α isopropyl ester but with less severe ocular 
side effects (41).

Bimatoprost reduced intraocular pressure in ocu-
lar normotensive and hypertensive monkeys over a 
0.001-0.1% dose range. A single dose and multiple 
dose ocular distribution/metabolism studies using [(3] 
H]-bimatoprost 0.1% were performed. Within the 
globe, bimatoprost concentrations were 10-100 folds 
higher in anterior segment tissues compared to the 
aqueous humor. Bimatoprost was overwhelmingly 
the predominant molecular species identified at all 
time points in ocular tissues, indicating that the intact 
molecule reduces intraocular pressure (42, 43).

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