S.Ü. Tıp Fak Derg, 2004; 20:47-54

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

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SUMMARY

Prostoglandins (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 uveascleral outflow in addition to their other mechanisms, but this has not yet been tested. Its potent ocular hypotensive action in primates, including man, Prostaglandin F_2 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 (EP_1, EP_2 EP_3), 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 exctracellular 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, PGD_2 PGE_2, $PGF_{2\alpha}$, PGI_2 and thromboxane A_2. 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)

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

Receptor	Natural prostaglandin	Synthetic agonist	Synthetic antagonist
DP	PGD_2	BW 245C	BW A 868C
EP*	PGE1/PGE_2	Sulprostone	AH 6809/SC 19920
FP	$PGF_{2\Delta}$	Fluprostenol	NA
IP	PGI_2	Iloprost	NA
TP	TxA_2	U 46619	BM 13.177
*EP receptors form three subtypes, donated as EP_1, EP_2 and EP_3. These are characterized as shown below			
EP_1	PGE_1/PGE_2	Sulprostone	AH 6809/SC-19220
EP_2	PGE_1/PGE_2	Butaprost	NA
EP_3	PGE_1/PGE_2	Sulprostone/enprostil	NA

NA: not available

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Geliş Tarihi : 17.03.2003 **Yayına Kabul Tarihi : 28.05.2003**

IOP reduction in dogs and monkeys is afforded by various receptor selective PG analogs implying the involvement of DP-, EP_1-, EP_2-, EP_3-, 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 PGD_2, PGE_2, $PGF_{2\Delta}$ and PGI_2 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 (EP_1, EP_2 or EP_3) in particular in the ocular hypotensive response to PGE_1 or PGE_2 has not been characterized.

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

Tablo 2. Classification of prostanoid receptors (Cayman – 2002).

Name	Receptor	Natural PG	Effect
15(R)-17-phenyltrinor prostaglandin $F_{2\alpha}$ isopropyl ester	FP	$PGF_{2\alpha}$	There are no published reports of the intra ocular hypotensive properties
15(S) Latanoprost	FP	$PGF_{2\alpha}$	There are no published reports of their biological activity and intra ocular hypotensive activity in particular of 15(S) Latanoprost.
15-keto Latanoprost	FP	$PGF_{2\alpha}$	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
Latanoprost (17-phenyl-13,14-dihydro $PGF_{2\alpha}$)	FP	$PGF_{2\alpha}$	Redusec IOP in glaucoma patients with few side effects.
Latanoprost (free acid)	FP	$PGF_{2\alpha}$	Is a prodrug form.
Latanoprost ethyl amide	FP	$PGF_{2\alpha}$	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.
17-triflouro metil phenyl 13-14 dihydrotrinor prostaglandin $F_{2\alpha}$	FP	$PGF_{2\alpha}$	It would act very much like the free acid of latanoprost.
17-phenyltrinor prostaglandin $F_{2\alpha}$ isopropyl ester	FP	$PGF_{2\alpha}$	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.
15-keto-17-phenyltrinor prostaglandin $F_{2\alpha}$	FP	$PGF_{2\alpha}$	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 .
17-phenyltrinor prostaglandin $F_{2\alpha}$ amide (Lumigan)	FP	$PGF_{2\alpha}$	Were recently introduced as alternative prostaglandin hypotensive prodrugs.
9-keto fluprostenol isopropyl ester (metabolit) of Travoprost	Acts primarly through the FP receptor and it has strong affinity for EP receptors	PGE_2	No studies on the pharmacology of this compound have been published.
15- (R)- 17 phenyltrinor prostaglandin $F_{2\alpha}$ isopropyl ester	FP	$PGF_{2\alpha}$	It is the Latanoprost-related isomer. There are no published report of th intraocular hypotensive properties of 15®-17 phenyltrinor $PGF_{2\alpha}$ isopropyl ester.

Lumula	FP		Lumula is a hybrid eicosanoid analog, which incorporates the docosanoid features of unoprostone as well as the prostamide features of bimatoprost. Lumula is a good tool for testing the validity of the alternate mechanism theories.
Prostaglandin $F_{2\alpha}$ alcohol	FP	$PGF_{2\alpha}$	The compound is reported to retain ocular hypotensive properties but the nature of the receptors, which mediate, is disputed.
Prostaglandin $F_{2\alpha}$ alcohol methyl ether	FP	$PGF_{2\alpha}$	The compound is reported to retain ocular hypotensive properties but the receptors, which mediate this activity, have not been clearly documented.
Prostaglandin $F_{2\alpha}$ ethyl amide (Bimatoprost-Lumigan)	FP	$PGF_{2\alpha}$	Has ocular hypotensive activity
Prostaglandin $F_{2\alpha}$ isopropyl ester	FP	$PGF_{2\alpha}$	When administered topically to the eyes of cynomolgus monkeys, a 5-µg dose reduces intraocular pressure bay 68% after the fourth day of treatment.
Prostaglandin $F_{2\alpha}$ methyl ester	FP	$PGF_{2\alpha}$	It was one of the first prostaglandin esters shown to have ocular hypotensive activity. This compound continues to be a standard by which other ocular hypotensive prostaglandin prodrugs are evaluated. The methyl ester is about 4-5 times more potent than the free acid $PGF_{2\alpha}$. A 2.5 µg dose of $PGF_{2\alpha}$- OMG applied to the eyes of cats results in a 6-8 mmHg reduction in IOP.
Unoprostone isopropyl ester (Rescula)	Docosanoid its biological activities independent of any known prostaglandin receptors.	$PGF_{2\alpha}$	The typical does of Rescula (one drop of 0.12% solution) is nearly 100 times that of Latanorost.
Iloprost	IP and EP_1	PGE_2, PGE_1	In whole animals, it acts as a vasodilatator hypotensive, antidiuretic and prolongs bleeding time. Human treatment for idiopathic pulmonary hypertension.
BW- A868C*	DP antagonist		It has virtually no effect on human TP,IP,EP_1,EP_2 and FP receptors, it antagonizes the accumulation of cAMP in rabbit non-pigmented ciliary epithelial cells
AL – 8810*	FP antagonist		The pharmacology of AL-8810 has not been published.
THG 113*	FP antagonist		It is effects on $FGF_{2\alpha}$- induced smooth muscle contraction
AL 3138*	FP antagonist		It is a unique and novel pharmacological tool to help characterize FP receptor- mediated functions.

* 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 prostanoid analogues with selectivity for individual receptor subtypes. They found that the highly selective FP receptor agonist fluprostanol caused no meaningful IOP changes in monkeys, cats and rabbits. They investigated the possibility that PGF2α 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 prostanoid receptor responsible for $PGF_{2\alpha}$ induced effects on primate intraocular pressure remains, however to be identified.

Waterburry (12) investigated two synthetic standards (sulprostone 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 EP_3 receptor agonists. For direct comparisons to be made, the effects of PGE, and PGE_2 on IOP were also studied. Compounds were administrated (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 PGE_2 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 EP_3, but not EP_2, FP or TP activity of these agonists correlated with the intraocular hypotensive effects. The stimulation of the EP_3 receptor resulted in a lowering of IOP in rabbits.

Toris (13) reported cats were treated twice daily for one week with PGA_2 (0.01%) to one eye and vehicle to the other. They found out PGA_2 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) F_2 alpha-isopropyl ester (IE), PGA_2, or PGA_2-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 uveascleral outflow accounts for a smaller portion of the total outflow (22, 23). These findings suggest that latanoprost and unoprostone reduce IOP through different hypotensive mechanism.

Krauss (16) suggest that thromboxane-mimetics and EP_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, SQ27986 (selective for the DP-receptor) and sulprostone (selective for EP_3 and EP_1 receptors) on IOP, pupil diameter and refraction in cynomolgus monkeys. SQ27986 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 SQ27986 and presumably DP-receptor stimulation in general, do not substantially increase uveoscleral outflow in the monkey eyes.

Sulprostone lowered 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 $PGF_{2\Delta}$ but the slight changes in refractive error are the opposite from the effects generally observed after $PGF_{2\Delta}$. Although $PGF_{2\Delta}$ 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_1 and EP_3 receptors.

Kelly (25) reported that, the ability of a number of prostaglandin $F_{2\Delta}$ ($PGF_{2\Delta}$) analogs to mobilize intracellular Ca^{2+} $[Ca^{2+}]i$ and to compete for $[^3H]PGF_{2\Delta}$ binding to prostaglandin $F_{2\Delta}$ receptors (FP) was evaluated. Radioligand binding studies measuring displacement of $[^3H]$ $PGF_{2\Delta}$ by a variety of FP prostaglandin analogs yielded the following rank order of affinities: travoprost acid [(+)-16-m-trifluorophenoxy tetranor $PGF_{2\Delta}$; (+)-fluprostenol] > bimatoprost acid (17-phenyl-trinor $PGF_{2\Delta}$)>>unoprostone (13, 14-dihydro-15-keto-20-ethyl $PGF_{2\Delta}$) = bimatoprost (17-phenyl-trinor $PGF_{2\Delta}$ ethyl amide) ≥ Lumigan (bimatoprost ophthalmic solution). In FP functional studies, travoprost acid bimatoprost acid, unoprostone, bimatoprost and lumigan concentration dependently stimulated $[Ca^{2+}]i$ 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 (11β-fluoro-15-epi-15-indanyl-tetranor $PGF_{2\Delta}$) (Ki = 0.6-1.3 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 $F_{2\Delta}$ receptors (FP) are G protein-coupled receptors that bind prostaglandin $F_{2\Delta}$ ($PGF_{2\Delta}$), resulting in the activation of an inositol phosphate (IP) second messenger pathway. Alternative mRNA splicing generates two FP receptor isoforms. These isoforms, designated FP_A and FP_B, are otherwise identical except for their carboxyl termini. FP_B is essentially a truncated version of FP_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 $PGF_{2\Delta}$-stimulated IP accumulation in transfected cells stably expressing the FP_A isoform but not in cells stably expressing the FP_B isoform. Whole-cell phosphorylation experiments showed a strong agonist-dependent phosphorylation of the FP_A isoform but little or no phosphorylation of the FP_B. Pretreatment of cells with bisindolylmaleimide I decreased $PGF_{2\Delta}$-stimulated phosphorylation of the FP_A isoform consistent with a PKC-dependent phosphorylation. In vitro phosphorylation of an FP_A carboxyl-terminal fusion protein by recombinant PKC_Δ showed that the carboxyl terminus of the FP_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 efficacius ocular hypotensive agent. It appears to mimic the activity of a newly discovered family of fatty acid amides, termed prostamides. 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 studied 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-PGF2a isopropyl ester is a prostaglandin analogue developed for glaucoma treatment and is as equally effective as $PGF_{2\alpha}$ on the FP/EP_1 and EP_3 receptors, but less potent on EP receptors. Interestingly, latanoprost exert very little effects on the EP_2 receptor (30). Topical administration of latanoprost substantially reduces IOP in monkeys and in glaucoma patients (31).

9 beta-[^{3}H] 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 intraocular 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 hypotensive 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-adrenergic antagonists may also suggest a lesser role of THC on the afferent vessels.

Pate(36) reported that attempts to indirectly determine if a neuronal cannabinoid (CB1) receptor mediates the intraocular pressure (IOP) reduction effects of arachidonoyl ethanolamide (AEA), its R-alpha-isopropyl analog, and the non-classical cannabinoid, CP-55,940. A series of these cannabinoids were dissolved in an aqueous 10-20% 2-hydroxypropyl-beta-cyclodextrin (2-HP-beta-CD) solution (containing 3% polyvinyl alcohol) and administered (25-62.5 microg)unilaterally to normotensive rabbit eyes. This was repeated on animals pre-treated with a subcutaneous injection (2.5 mg/kg) of the highly specific CB_1 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 subcutaneous pretreatment of the rabbits with the CB_1 receptor antagonist, but the IOP properties of AEA remained unchanged. SR 141716A administered alone, elevated the IOP of both eyes. A CB_1 receptor seems involved in the IOP reduction induced by either R-alpha-isopropyl anandamide or CP-55,940. However, AEA apparently functions through a different 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 glaucoma 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 uveascleral outflow in the normotensive eyes, but not in the hypertensive eyes.

Travoprost produced a lower incidence of ocular irritation than $PGF_{2\alpha}$ isopropyl ester at a dose of 1 microg 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 microg. In the ocular hypertensive monkey, b.i.d. application of 0.1 and 0.3 microg of travoprost 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 discomfort at doses up to 1 microg. Travoprost is a promising ocular hypotensive prostaglandin FP derivative that has the ocular hypotensive efficacy of $PGF_{2\alpha}$ isopropyl ester but with less severe ocular side effects (41).

Bimatoprost reduced intraocular pressure in ocular 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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