L E C T U R E

From $PGF_{2\alpha}$-Isopropyl Ester to Latanoprost: A Review of the Development of Xalatan

The Proctor Lecture

Johan Wilhelm Stjernschantz

The research that led to the concept of using prostaglandins for reduction of intraocular pressure (IOP) has been discussed by Bito and goes back to the early 1980s, when it was shown that $PGF_{2\alpha}$ effectively reduces IOP in monkeys.[1] Because the IOP-reducing effect in primates was found to be profound and of long duration, it was of obvious interest to investigate whether prostaglandins could be developed into drugs for glaucoma treatment. A fruitful collaboration between Columbia University (New York, NY) and Pharmacia (Uppsala, Sweden), a pharmaceutical company, was initiated. As a result of the collaboration, a new glaucoma drug Xalatan was developed. The purpose of this article is to present a review of the research that lead to the identification of latanoprost, and the development of Xalatan. Some relevant recent and previously unpublished data have been included as well. The experimental protocols of all animal studies performed complied with the tenets of the ARVO Statement on the Use of Animals in Ophthalmic and Vision Research, and all protocols were submitted for review and approval to the local Ethics Committee for Animal Experimentation. Protocols for clinical studies were submitted to the appropriate Ethics Committee/Internal Review Board and the Declaration of Helsinki (1964) with subsequent revisions was adopted. Details concerning the experimental procedures of the previously unpublished results are given in the figure and table texts.

$PGF_{2\alpha}$-Isopropyl Ester as a Prototype Prostaglandin Drug for Glaucoma Treatment

The first approach to render prostaglandins suitable for glaucoma treatment was esterification of the carboxylic acid to improve the bioavailability[2] and reduce the side effects. Several esters of $PGF_{2\alpha}$ were synthesized and tested for IOP-reducing effect and side effects.[3] One of the best of these prodrugs of $PGF_{2\alpha}$ was the isopropyl ester (IE), but many other carboxylic acid esters, and di-, tri-, and tetra-esters and lactones of $PGF_{2\alpha}$ were prepared and tested in addition (Bito LZ, Resul B, unpublished results, 1985). Similar experiments were also performed by researchers at Allergan Pharmaceuticals (Irvine, CA).[4] Other companies (e.g., Ueno Fine Chemicals Industry, Osaka, Japan, and Alcon Laboratories, Fort Worth, TX) subsequently adopted the isopropyl ester prodrug concept for their respective prostaglandin analogues (isopropyl unoprostone and travoprost, respectively).

$PGF_{2\alpha}$-IE is a very efficacious and potent IOP-reducing agent in cats, dogs, and monkeys.[2,5–7] Comparable reductions of IOP with $PGF_{2\alpha}$ tromethamine salt requires a 10 to 100 times higher dose in monkeys.[2,8–10] Thus, esterification of $PGF_{2\alpha}$ with isopropanol increased the bioavailability substantially. Overall, $PGF_{2\alpha}$-IE was found to be a very good IOP-reducing agent in many species except rabbits, in which a pressure increase frequently is induced by a breakdown of the blood–aqueous barrier. It is interesting that whereas cats exhibited distinct signs of ocular pain and discomfort (e.g., closure of the lids and lacrimation) unanesthetized monkeys usually did not (Stjernschantz J, unpublished results, 1988). In addition, in cats and dogs $PGF_{2\alpha}$ and its esters are potent miotics.[11]

In the first clinical trial with $PGF_{2\alpha}$-IE, which had the character of a pilot test, no or a minimal IOP-reducing effect was observed in patients with glaucoma, probably because difficult cases were selected, refractory to all medical treatment (unpublished results, Pharmacia). Despite these discouraging results Villumsen and Alm,[12] in cooperation with Pharmacia, started a systematic investigation to determine the IOP-reducing effect and side effects of $PGF_{2\alpha}$-IE and found that the drug indeed effectively reduced IOP in a dose-dependent manner in healthy volunteers. However, the IOP-reducing effect was accompanied by conjunctival hyperemia and ocular irritation similar to the side effects seen in studies with the tromethamine salt of $PGF_{2\alpha}$.[13,14] The highest dose (10 μg) of $PGF_{2\alpha}$-IE caused pain and photophobia in all individuals.[12] A dose of 0.5 μg twice daily was chosen for further studies in patients, and this dose, as well as a dose of 1 μg twice daily, was found to reduce IOP significantly, alone and in combination with timolol.[15–18]

However, many patients reported side effects such as foreign-body sensation and conjunctival hyperemia, and it became questionable whether $PGF_{2\alpha}$-IE would offer any advantage over the already-established glaucoma medications. A particular problem was the irritative response to the drug. In animal experiments, it has been shown that $PGF_{2\alpha}$-IE induces albumin leakage in the iris and the ciliary body of monkeys at a dose of 1 μg,[19] and it is possible that the 10 times higher dose previously used in healthy individuals[12] induces edema in the anterior uvea that causes pain and photophobia.

Effect of $PGF_{2\alpha}$-IE on the Uveoscleral Outflow Mode of Action

The first evidence that $PGF_{2\alpha}$ and its isopropyl ester reduces IOP through a mechanism based on increased uveoscleral outflow came from the studies by Crawford and Kaufman[20] and Nilsson et al.[6] Both research groups independently of each other found evidence for increased uveoscleral outflow of aqueous humor in monkeys treated with $PGF_{2\alpha}$ tromethamine salt or $PGF_{2\alpha}$-IE and no or minimal effect on the conventional

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Submitted for publication July 17, 2000; accepted September 8, 2000.

Commercial relationships policy: F, I, P. (The author is a former employee of Pharmacia and is a recipient of a research grant from Pharmacia, but has no commercial interest in Xalatan.)

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TABLE 1. Effects of $PGF_{2\alpha}$-IE, $PGF_{2\beta}$-IE, and 11-epi-$PGF_{2\alpha}$-IE on IOP, Pupil Diameter, and Nociception in Cats and on IOP in Monkeys

	Cat				Monkey		
Prostaglandin Analogue	Dose (μg)	Reduction in IOP (mm Hg)	Reduction in Pupil Diameter (mm)	Irritation*	Dose (μg)	Reduction in IOP (mm Hg)	FP Receptor EC_{50} Value (moles/l)
$PGF_{2\alpha}$-IE	1.0	-7.5 ± 1.3‡	-9.3 ± 0.4†	2.7 ± 0.2†	3.0	-2.5 ± 0.3†	1.0×10^{-8}
$PGF_{2\beta}$-IE	1.0	-8.3 ± 1.5‡	0.0 ± 0.0	1.5§	1.5	-1.1 ± 0.8	5.6×10^{-6}
11-*epi*-$PGF_{2\alpha}$-IE	1.0	0.2 ± 0.5	-7.0 ± 0.7†	1.0§	2.4	-2.0 ± 0.9	3.3×10^{-8}

The values are based on the maximum difference between the experimental and contralateral control eyes (mean ± SEM; $n = 5$–6). The FP receptor EC_{50} values are based on results of in vitro tests performed on cat irides with the corresponding prostaglandin acids. Partly reproduced, with permission, from Resul et al., *Surv Ophthalmol.* 1997;41(suppl):S47–S52.

* Arbitrary scale of 0 to 3 (see Fig. 3).

† $P < 0.001$.

‡ $P < 0.005$.

§ Estimated mean value.

outflow.[6,20,21] Indirect evidence for a similar mechanism in humans was also obtained in two separate studies: $PGF_{2\alpha}$-IE was not found to have any effect on aqueous humor production or outflow facility.[12,22] Thus, the most reasonable explanation for the IOP reduction was increased uveoscleral outflow, although it could not be excluded that the drug may have reduced the episcleral venous pressure, too. It is important to note that in neither of the two clinical studies was any evidence found of a significant effect of $PGF_{2\alpha}$-IE on the blood–aqueous barrier.[12,22]

Rationale of Receptor Selectivity for Elimination of Side Effects

The preclinical and clinical studies with $PGF_{2\alpha}$-IE demonstrated that prostaglandins of the F type could be useful in the treatment of glaucoma, but it was not realistic to develop $PGF_{2\alpha}$-IE into a glaucoma drug for broader use, because of the side effects. Patients with severe disease could have endured treatment with the drug for some time. The question thus arose of whether it would be possible to separate the IOP-reducing effect from the side effects—primarily the irritative and hyperemic effects—by changing the receptor profile of $PGF_{2\alpha}$ through chemical modification. It should be recalled in this context that the classification of the prostanoid receptors in the mid 1980s was somewhat ambiguous, based on conventional pharmacologic experiments only.[23–25] However, early experiments that we had performed with two epimers of $PGF_{2\alpha}$-IE, namely $PGF_{2\beta}$-IE and 11-*epi*-$PGF_{2\alpha}$-IE indicated that the miotic and IOP responses to $PGF_{2\alpha}$-IE could be distinctly separated by these two epimers in cats (Table 1). $PGF_{2\beta}$-IE reduced IOP with no miotic effect, whereas 11-*epi*-$PGF_{2\alpha}$-IE was a potent miotic with little effect on IOP. Furthermore, the epimers also differed from $PGF_{2\alpha}$-IE with respect to the nociceptive response (Table 1) and the hyperemic response, $PGF_{2\beta}$-IE, being a much stronger vasodilator than both $PGF_{2\alpha}$-IE and 11-*epi*-$PGF_{2\alpha}$-IE (unpublished results; Pharmacia). Thus, it appeared possible to separate the different ocular responses from each other, at least partly, and there was also an indication that the FP prostanoid receptor, which mediates miosis in cats, may be involved at least partly in IOP reduction in monkeys.[26] (Table 1).

A critical aspect in the success of the screening work was the selection of appropriate animal models that would allow extrapolation of the results to the human eye. The cat eye seemed very unspecific, in that IOP reduction was brought about by widely different prostaglandin analogues (e.g., $PGF_{2\alpha}$, $PGF_{2\beta}$, PGE_2, PGA_2, PGB_2, and PGD_2). Therefore, we regarded the cat eye as somewhat unpredictable with respect to the IOP the nociceptive and miotic effects, whereas conscious cynomolgus monkeys were used to study the IOP-reducing effect. However, because young healthy monkeys usually have low IOP, often around 11 to 15 mm Hg, the test model was not ideal but was good enough to confirm whether an analogue had an IOP-reducing effect. The hyperemic effect was studied in albino rabbits, but there were no attempts to study anything else in the rabbit, because the rabbit eye is known to react very atypically to prostaglandins.[27–29] Thus, the selection of adequate animal models was of paramount importance for the success of the project.

Structure–Activity Approach and Identification of Phenyl-Substituted Prostaglandin Analogues

The first approach to modifying $PGF_{2\alpha}$ included various alterations of the carboxylic acid end of the molecule. The alterations comprised, for example, the alcohol and simple esters but generally did not result in any clear-cut improvement of the pharmacologic profile of $PGF_{2\alpha}$. The second approach was to change the stereochemistry, and the functional groups in the cyclopentane ring. Although this yielded some interesting analogues that offered certain advantages over $PGF_{2\alpha}$, such as 11-*epi*-$PGF_{2\alpha}$,[26] modifications of the cyclopentane ring resulted in no real breakthrough. The third approach was to alter parts of the ω chain (e.g., the double bond between carbons 13 and 14 and the 15-hydroxyl group) and to substitute part of the chain. However, it was well known that the 15-hydroxyl group is essential for biologic activity of prostaglandins, and dehydrogenation of the hydroxyl group results in marked loss of biologic activity.[30–31] Thus, the approach taken by the researchers of Ueno Fine Chemicals Industry (Osaka, Japan) to reduce the side effects of $PGF_{2\alpha}$ by preparing the 13,14-dihydro-15-keto metabolite, or modifications of this metabolite (e.g., isopropyl unoprostone) renders molecules with significantly reduced potency.[32]

Among a group of different ω-chain–modified prostaglandin analogues, we quite unexpectedly noted that 17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$-IE induced marked miosis in the cat without concomitant irritation, which almost all other prostaglandin analogues had induced. Although there was no significant effect of the analogue on IOP in cats, conceptually, the combination of marked miosis with absence of nociception demonstrated that it was possible to eliminate the nociceptive effect without losing pharmacologic activity. In contrast to cats,[33] monkeys responded to the compound with satisfactory IOP reduction.[34–35] The compound, which can be regarded as the breakthrough, was assigned the code name PhDH100A and became the lead compound

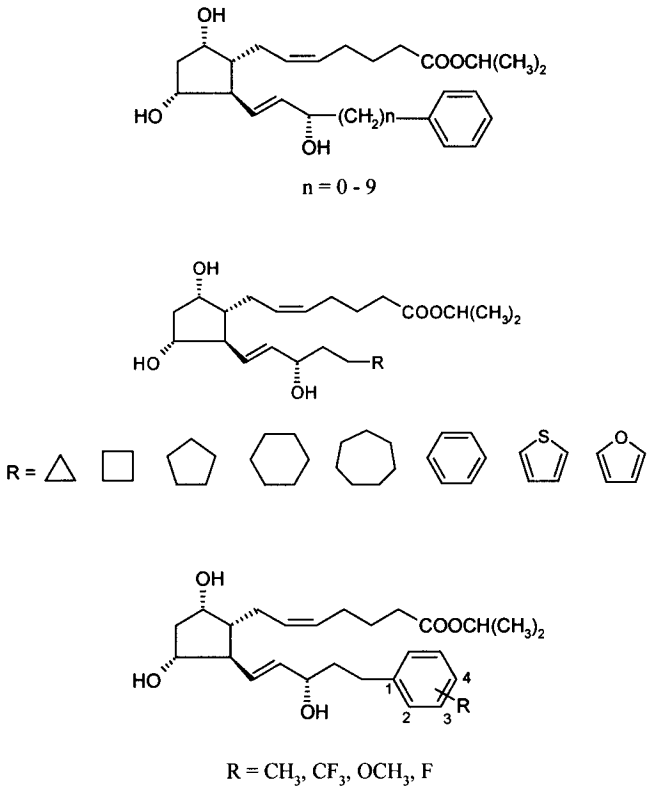

FIGURE 1. Series of ring-substituted analogues of $PGF_{2\alpha}$-isopropyl ester tested for effects in the eye to determine the importance of ω-chain length, ring structures, and substituents in the phenyl ring.

logues in the screening for an optimal prostaglandin analogue for glaucoma treatment.

Importance of ω-Chain Length, Ring Structures, and Substituents

The identification of 17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$-IE lead to medicinal chemistry experiments that were of obvious interest to perform to understand the critical elements in the molecules for attaining efficacy and selectivity in the eye. Three aspects seemed particularly relevant to study: (1) the influence of the ω-chain length, (2) the influence of different ring structures, and (3) the influence of substituents in the ring structure on the pharmacologic profile of the new analogues.

Influence of ω-Chain Length on Pharmacologic Profile

This aspect was studied in detail by attaching a terminal phenyl ring to carbons 15-24 (Fig. 1). The analogues were studied in cats with emphasis on the miotic and nociceptive responses. Of note, attaching the aromatic ring structure to carbon 17 of the prostaglandin skeleton yielded an optimal compound, in that the FP receptor function, as evident from the miotic response, was not compromised, whereas the nociceptive response was completely abolished[34] (Table 2). In bizarre contrast, 16-phenyl-17,18,19,20-tetranor-$PGF_{2\alpha}$-IE with one additional carbon atom removed from the ω chain caused significant irritation, albeit less than $PGF_{2\alpha}$-IE. Elongation of the ω chain beyond carbon 17 with a terminal phenyl ring attached, reduced the biologic activity[34] (Table 2). However, it is noteworthy that most analogues with a terminal ring structure exhibited considerably less nociceptive effect than $PGF_{2\alpha}$-IE. Substitution of carbon 17 with oxygen afforded a compound (16-phenoxy-17,18,19,20-tetranor-$PGF_{2\alpha}$-IE) with similar pharmacologic profile to that of 17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$-IE (unpublished results; Pharmacia).

Influence of Different Ring Structures on the Pharmacologic Profile

A large number of compounds with different ring structures from cyclopropyl to cycloheptyl and aromatic ring structures, such as phenyl, thiophen, and furyl, attached to carbon 17 (Fig. 1) were prepared and tested. Overall, these analogues exhibited an improved side-effect profile compared with $PGF_{2\alpha}$-IE, albeit with somewhat different pharmacologic activity. Thus it appears that many different terminal ring structures attached to carbon 17 in the ω chain reduce the side effects of $PGF_{2\alpha}$-IE.

Influence of Substituents in the Ring Structure on the Pharmacologic Profile

Compounds with various substitutions in the phenyl ring (Fig. 1) were also prepared and tested for pharmacologic activity.[26,34] Introduction of a methyl group into the *ortho* (2) or *meta* (3) position in the phenyl ring did not appreciably change the miotic activity of 17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$-IE, whereas introduction of the methyl group into the *para* (4) position dramatically reduced the activity.[26,34] Obviously, the methyl group in the *para* position induces a steric hindrance in the receptor ligand interaction. Introduction of an electron-attracting trifluormethyl group into the *ortho* or *para* position in the phenyl ring reduced the activity of the compound,

TABLE 2. Effect of Phenyl-Substituted $PGF_{2\alpha}$-IE Analogues with Different ω-Chain Lengths on IOP, Pupil Diameter, Nociception, and Conjunctival Hyperemia

		Cat		
Prostaglandin Analogue	Monkey Reduction in IOP (mm Hg)	Reduction in Pupil Diameter (mm)	Irritation* (0–3)	Rabbit Hyperemia* (1–5)
16-Phenyl-17,18,19,20-tetranor-$PGF_{2\alpha}$-IE	−3.9 ± 0.4†	−1.0 ± 0.0†	2.2 ± 0.3†	ND
17-Phenyl-18,19,20-trinor-$PGF_{2\alpha}$-IE	−3.9 ± 0.4†	−9.7 ± 0.3†	0.0 ± 0.0	1.8 ± 0.3‡
18-Phenyl-19,20-dinor-$PGF_{2\alpha}$-IE	−0.6 ± 0.2§	−4.3 ± 0.6†	0.7 ± 0.1†	0.3 ± 0.7
19-Phenyl-20-nor-$PGF_{2\alpha}$-IE	−0.6 ± 0.2§	−2.5 ± 0.6‡	1.3 ± 0.2‡	0.6 ± 0.2§

The values are based on the maximum difference between the experimental and contralateral control eyes. The dose was 3 μg in monkeys, 1 μg in cats, and 0.5 μg in rabbits (mean ± SEM; n = 5–6; statistical significances determined by paired t-test). ND, not determined.

* Arbitrary scale.

† $P < 0.001$.

‡ $P < 0.01$.

whereas introduction of the group into the *meta* position only slightly reduced the activity.[26,34] Substituting fluorine for the trifluormethyl in the *ortho*, *meta*, or *para* position afforded compounds with marked miotic effect and no or very little irritant effect in the cat eye, thus indicating that the trifluormethyl group may also partly change the pharmacologic activity through a steric effect.[26,34] Introduction of an electron-donating methoxy group into the *ortho* or *para* position markedly reduced miotic activity, whereas introduction of the group into the *meta* position only slightly reduced miotic activity.[26,34] The 16-(4-methoxy)-phenyl-17,18,19,20-tetranor $PGF_{2\alpha}$-IE analogue had virtually no irritant effect in the cat eye in contrast to 16-phenyl-17,18,19,20-tetranor-$PGF_{2\alpha}$-IE (unpublished results, Pharmacia). Thus, it appears that the *para* position, and to some extent the *ortho* position, in the phenyl ring are sensitive to steric hindrance, whereas the *meta* position is much less vulnerable. However, in the *ortho* position electrochemical forces may be important, at least in part, because an electron-attracting trifluormethyl group reduces the activity in contrast to a neutral methyl group.

Overall, the structure–activity studies indicated that the ring structure on the ω chain is of paramount importance for reducing the side effects of $PGF_{2\alpha}$-IE, and furthermore that a large number of modifications of the ring structure are possible, still affording useful compounds in the eye.[26,34–36]

Saturation of the 13,14-*trans* double bond of 17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$-IE was found to further improve the receptor profile somewhat, and 13,14-dihydro prostaglandin analogues in addition exhibited improved chemical stability. The 13,14-dihydro-15*R*,*S*-17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$-IE analogue was selected as the new candidate drug, and the compound was given the code name PhXA34. Because the 15R epimer is more potent than the 15*S* epimer, with time the 15*R* epimer (PhXA41) became the final candidate drug. It was given the generic name latanoprost and is the active principle in Xalatan. The chemical structures of $PGF_{2\alpha}$-IE, 17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$-IE, PhXA34, and latanoprost (PhXA41) are presented in Figure 2.

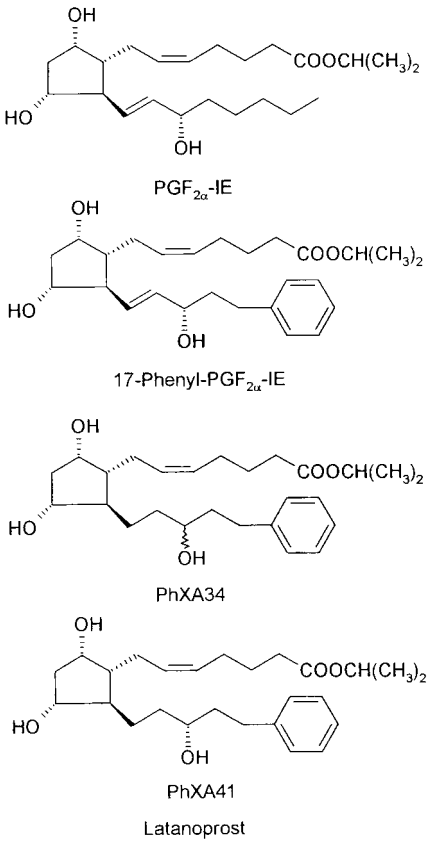

FIGURE 2. Chemical structures of $PGF_{2\alpha}$-IE, 17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$-IE, 13,14-dihydro-15*R*, *S*-17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$-IE (PhXA34), and 13,14-dihydro-15*R*-17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$-IE (latanoprost).

Latanoprost

As is obvious from the structure–activity studies, the reason for the good therapeutic index of latanoprost in the eye is its pharmacologic receptor profile. It can be seen in Table 3 that latanoprost acid is a much more selective FP prostanoid receptor agonist than $PGF_{2\alpha}$. In practical terms it is even more selective than 17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$ because it spills less over on the EP_1 and TP receptors (Table 3). It is also apparent that latanoprost acid is a full agonist on the FP receptor, and full or near full agonist on the EP_1 and EP_3 receptors, but has no, or only weak effect on prostanoid receptors EP_2, DP, IP, and TP (Table 3). In comparison 17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$, with the 13,14 double bond intact, is a full agonist on the FP and EP_1 receptors, and a partial agonist on the TP receptor, but has no, or only weak effect on the other receptors (Table 3). Thus, increasing the flexibility of the ω chain by saturating the 13,14 double bond has relatively little effect on the interaction with the FP receptor, but reduces the potency on the EP_1 and TP receptors, and increases the capacity to stimulate the EP_3 receptor, albeit only at very high concentrations.

Latanoprost has virtually no IOP-reducing effect in cats or rabbits, but induces a moderate IOP reduction in conscious normotensive monkeys as measured 3 to 6 hours after topical application. During continuous treatment with 3 μg once daily for 5 days the IOP reduction lasted around the clock (unpublished results; Pharmacia). In ocular hypertensive monkeys a

The absence of effects in cats and rabbits may be due to several factors—for example, different anatomy of the ciliary muscle and aqueous humor outflow pathways compared with primates, and the absence of expression or different coupling of FP receptors in the ciliary muscle. Of note, recently it was demonstrated that the prostanoid receptor EP_1 seems to mediate the IOP reduction of $PGF_{2\alpha}$ in the cat.[38]

Mode of Action

Thorough pharmacodynamic studies in cannulated monkey eyes were performed to investigate the mode of action of latanoprost, because the mechanism could differ from that of $PGF_{2\alpha}$-IE due to the different receptor profiles of the compounds. Cynomolgus monkeys were treated for 5 days topically on one eye with 3 μg latanoprost daily; the other eye received vehicle only and served as the control. A detailed description of the pharmacodynamic method has been presented.[39] The results showed that latanoprost had a statistically significant effect on the uveoscleral outflow, which increased by approximately 60% compared with the contralateral control eye.[39,40] Neither the trabecular outflow of aqueous humor, nor the total outflow facility changed during latanoprost treatment.[39,40]

The reason for the increase in flux of aqueous humor through the ciliary muscle during prostaglandin treatment has been studied in detail at the cellular level by Lindsey et al.[41–47] $PGF_{2\alpha}$ seems to increase the expression of c-Fos in human ciliary muscle cells, which in turn may increase the expression of matrix metalloproteinases (MMPs)—for example, MMP-1, MMP-2, MMP-9 and MMP-10—as well as their precursors,[42,43]

TABLE 3. Potency Based on EC_{50} Values and Estimated Efficacy of $PGF_{2\alpha}$, 17-Phenyl-18,19,20-trinor-$PGF_{2\alpha}$ (17-Phenyl-$PGF_{2\alpha}$), and Latanoprost Acid as Measured in Functional Receptor Assays[24]

Prostaglandin Analogue	FP		EP_1		EP_2		EP_3		IP/DP		TP	
	Potency	Efficacy	Potency	Efficacy	Potency	Efficacy	Potency	Efficacy	Potency	Efficacy	Potency	Efficacy
$PGF_{2\alpha}$	1.2×10^{-8}	100	3.2×10^{-7}	100	6.4×10^{-6}	100	1.6×10^{-7}	100	$>10^{-4}$	0	$>10^{-4}$	~20
17-Phenyl-$PGF_{2\alpha}$	4.5×10^{-9}	100	6.5×10^{-7}	100	$>10^{-4}$	0	$>10^{-4}$	0	$>10^{-4}$	0	3.4×10^{-5}	~50
Latanoprost acid	1.0×10^{-8}	100	5.0×10^{-6}	100	$>10^{-4}$	0	2.8×10^{-5}	~80	$>10^{-4}$	0	$>10^{-4}$	0

The receptor assays were based on the following tissues: FP, cat iris sphincter; EP_1, bovine iris sphincter in the presence of GR32191B; EP_2, electrical stimulation of guinea pig ileum; EP_3, electrical stimulation of guinea pig vas deferens; IP/DP, prevention of adenosine diphosphate-induced guinea pig platelet aggregation; and TP, guinea pig platelet aggregation. For estimation of efficacy, the compounds were compared with $PGF_{2\alpha}$ (FP), PGE_2 (EP_1, EP_2, and EP_3), carbaprostacyclin (IP), BW245C (DP), and U-46619 (TP). Potency is expressed in moles per liter and efficacy as percentage.

matrix components toward catabolism.[44–46] $PGF_{2\alpha}$-IE was found to reduce collagens I, III, and IV in the ciliary muscle and adjacent sclera of the monkey after topical treatment with 2 μg twice daily for 5 days.[47] Similar results were obtained by Ocklind[48] who demonstrated a decrease in collagens I, III, and IV; laminin; fibronectin; and hyaluronan in human ciliary muscle cell cultures exposed to latanoprost acid in parallel with an increase in MMP-2 and MMP-3. She also found evidence for reduced collagens IV and VI levels in the ciliary muscle after 10 days of topical treatment with 3 μg latanoprost daily in monkeys.[48] Furthermore, evidence for a change in the shape of ciliary muscle cells was also found after exposure to latanoprost acid in vitro, with alterations in the actin and vinculin localization in the cells.[39] Thus, the results indicate that latanoprost may have complex effects on ciliary muscle, the net effect being increased percolation of aqueous humor through the tissue.

Vascular Effects of Latanoprost

Both the local and systemic vascular effects of latanoprost have been studied in detail. In the rabbit eye latanoprost induced no or minimal change in blood flow,[19] in sharp contrast to $PGF_{2\alpha}$-IE, which induced marked increase in blood flow to the surface structures and the anterior uvea after topical application.[49] The hyperemic effect of $PGF_{2\alpha}$-IE seems to be based on a release of nitric oxide (NO), and apparently the mechanism leading to NO release does not involve FP receptors.[49] Of interest, sensory denervation by electrocoagulation of the ophthalmic nerve, almost completely abolished the hyperemic effect of $PGF_{2\alpha}$-IE in rabbits, implying that the effect is nerve-mediated.[50] This fits well with the absence of nociceptive effect of FP prostanoid receptor agonists such as latanoprost. By using selective agonists we studied which of the prostanoid receptors mediate the nociceptive response to prostaglandins in the cat eye and found that the FP and EP_2 receptors are of little or no importance (Fig. 3). Stimulation of the DP, IP, EP_1, and EP_3 receptors, on the contrary, induced a nociceptive response in the cat eye (Fig. 3). Whether $PGF_{2\alpha}$-IE–induced conjunctival hyperemia in humans also involves sensory nerves is unknown, but it is quite possible.

Latanoprost and PhXA34 tested at a dose of approximately four times the clinical dose of latanoprost in Xalatan had a negligible effect on the regional blood flow in the monkey eye after topical application.[51] Neither was any effect seen on capillary permeability to albumin in the monkey eye.[51] Intravenous injection of latanoprost in escalating doses of up to 6 μg/kg body weight had no statistically significant effect on the uveal or retinal blood flow in monkeys, although a tendency toward increased blood flow was observed (Table 4).[19] In aphakic monkey eyes with intact posterior lens capsule, latanoprost induced no capillary leakage in the retina as studied with fluorescein angiography during 6 months of treatment, and similar results were also obtained during shorter treatment periods in pseudophakic patients.[52] Thus, it appears that the

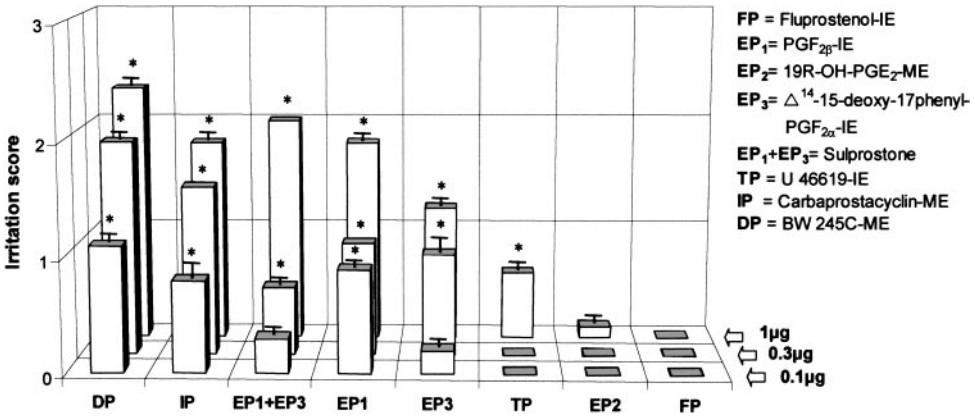

FIGURE 3. Maximum nociceptive effect of selective prostanoid receptor agonists in the cat eye. The agonists were applied unilaterally at three different doses. The irritation was estimated by observing the animals for 6 hours after administration of the test substances. An arbitrary scale of 0 to 3 was used: 0, no signs of ocular irritation; 1, slight; 2, moderate; and 3, marked signs of irritation as evident from complete lid closure and lacrimation. The complete name of the EP_3 agonist is 13,14-dihydro-Δ^{14}-*trans*-15-deoxy-17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$-IE, and the compound is not a full agonist on the EP_3 receptor. Thus, the effect on the EP_3 receptor may be underestimated. Mean ± SEM; n = 4–6 for each compound and dose;

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Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.