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PHARMACOLOGICAL MECHANISMS, CLINICAL EFFECTIVENESS, AND SIDE-EFFECTS OF PROSTAGLANDIN ANALOGUES AS ANTI-GLAUCOMA AGENTS

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Prostaglandin (PG)-related ophthalmic solutions, which only recently became available for clinical use, are currently the most widely used solutions in the treatment of glaucoma, because they have excellent ocular hypotensive effects with little adverse effects. With respect to the pharmacological mechanism of action of these solutions, the mechanism of intraocular pressure (IOP) reduction for latanoprost, the first drug in this class to become available, is to promote the outflow of aqueous humor through the uveoscleral route, an important aqueous humor outflow tract. Molecular and cellular studies have shown that latanoprost affects the extracellular matrix metabolism in the uveoscleral route. For other PG-related ophthalmic solutions, there is no consensus opinion on their effects on the aqueous humor outflow tract, and how they reduce the IOP remains largely unclear. The docosanoid, isopropyl unoprostone, has excellent ocular hypotensive effects, despite having extremely low affinities to the known PG receptors. Many basic and clinical studies have demonstrated that PG-related ophthalmic solutions themselves cause not only a decrease in the IOP, but also induce endogenous PGs which could lead to secondary effects that may account in part for the IOP reduction. PG-related ophthalmic solutions have essentially no clinically important systemic adverse effects, but often have local adverse effects. The most characteristic is the pigment deposition in the iris or eyelid. Corneal epitheliopathy is also relatively common. In addition, as an adverse effect that affects vision, cystoid macular edema can be seen. Current studies are aimed at elucidating the mechanisms of development of these adverse effects, and thus to establish measures to prevent them. We compare the mechanisms of action of PG-related ophthalmic solutions and review the adverse effects and their mechanisms.
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HISTORY OF DEVELOPMENT OF PROSTAGLANDIN-RELATED OPHTHALMIC SOLUTIONS

In 1981, Camras and Bito (1) demonstrated that ophthalmic administration of prostaglandin (PG)$F_{2\alpha}$ caused a decrease in the intraocular pressure (IOP). However, because $PGF_{2\alpha}$ caused initially an increase in the IOP and also induced severe local irritation, further studies were conducted to overcome these side effects. These studies led to the development and eventual clinical use of the $PGF_{2\alpha}$-related agent, latanoprost, as the first anti-glaucoma solution in this class. Later, studies by Goh *et al* (2) in Japan led to the development of the docosanoid, isopropyl unoprostone (referred to unoprostone thereafter), which was approved for clinical use in Japan in 1994. Thereafter, the prostanoid, bimatoprost, became available in 1997 and another $PGF_{2\alpha}$-related agent, travoprost, became available in 1999.

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Currently, the above four PG-related ophthalmic solutions are in clinical use in the US. The structures of these compounds are shown in Figure 1.

STRUCTURAL FEATURES AND COMPARISON OF PG-RELATED OPHTHALMIC SOLUTIONS

The IOP is determined by the production and outflow of the aqueous humor, and as indicated in Figure 2, humans have two aqueous humor outflow routes. The aqueous humor is produced by the ciliary body epithelial cells, passes through the pupillary region and flows towards the iridocorneal angle. The outflow tract from the iridocorneal angle through the trabecular meshwork and the canal of Schlemm to the venous circulation is called the conventional outflow route, and this is the major aqueous humor outflow tract occupying more than 90% of total outflow in normal eye. The system from the iridocorneal angle between the ciliary muscle bundles and the subscleral space is called the uveoscleral outflow route. In normal eyes, it accounts for less than 10% of the total aqueous humor outflow. The aqueous humor outflow from the conventional route changes depending on the IOP, but the efficiency of the uveoscleral outflow is unaffected by the IOP.

The widely used conventional glaucoma treatment drugs,

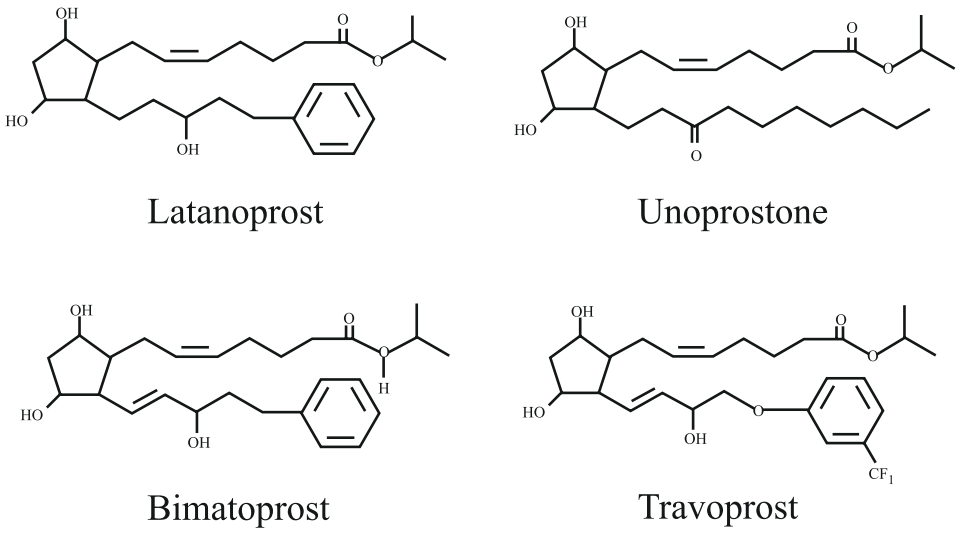


Figure 1. *Structures of PG-related ophthalmic solutions.*

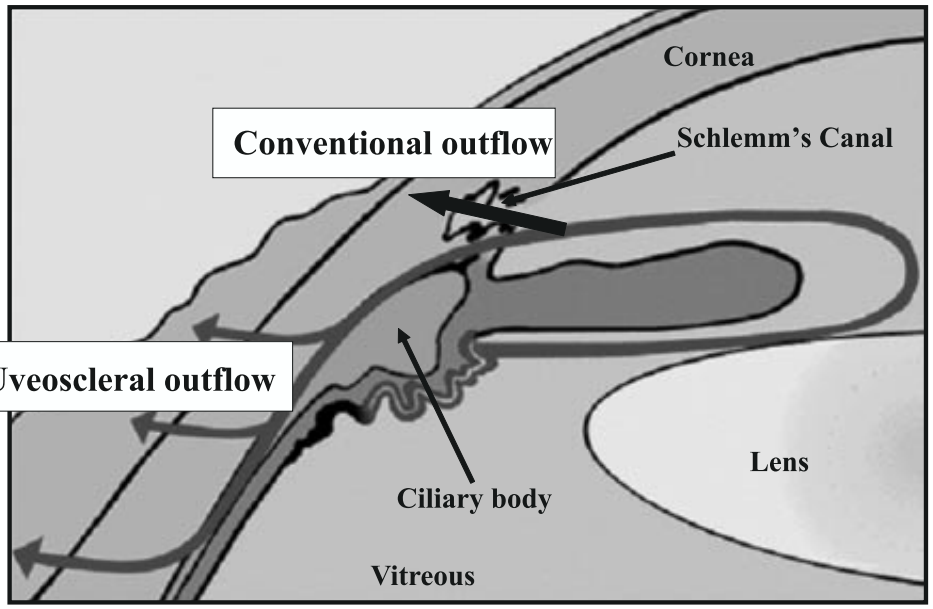


Figure 2. *Scheme of major aqueous outflow routes.*

beta-blockers and carbonic anhydrase inhibitors, inhibit the production of the aqueous humor from the ciliary body epithelial cells and decrease the IOP. Pilocarpine increases the conventional outflow and decreases the IOP. The major mechanism of IOP reduction by the PG-related ophthalmic solutions is thought to be the promotion of the uveoscleral outflow, but some PG-related ophthalmic solutions have also been suggested to increase the conventional outflow, although the details are unknown. This review will mainly summarize the pharmacological mechanism of action of latanoprost in reducing the IOP, since much progress has been made in the research of this drug. Although the PG-related anti-glaucoma ophthalmic solutions have only few systemic adverse effects, they are known to cause local adverse effects, such as increased pigmentation of the iris, hypertrichosis of the eyelids, and cystoid macular edema. This review also summarizes the mechanisms underlying these adverse effects.

MECHANISM OF IOP REDUCTION BY LATANOPROST

Latanoprost was developed on the basis of studies by J. Stjernschantz and L. Bito, and its clinical use began in North America and Europe in 1995 (3). Its structure is similar to $PGF_{2\alpha}$ (Fig. 1) and has a high $PGF_{2\alpha}$ (FP) receptor selectivity. Of the aqueous humor outflow routes indicated in Figure 2, latanoprost has no effect on the conventional outflow but promotes the uveoscleral outflow of the aqueous humor, thereby decreasing the IOP. The promotion of the uveoscleral outflow of the aqueous humor has been attributed to (*i*) ciliary muscle relaxation, resulting in greater gaps between the muscle bundles, thus allowing greater outflow of the aqueous humor, and (*ii*) remodeling of the extracellular matrix (ECM) surrounding the ciliary muscle bundles, thus promoting the outflow of the aqueous humor through the ECM. However, a number of reports contradict the former theory. Namely, although pilocarpine can increase muscle contraction and decrease the uveoscleral outflow, it does not interfere with the IOP lowering effects when used concurrently with latanoprost, but rather has synergistic effects to decrease the IOP. Further, the latanoprost-mediated relaxation of the ciliary muscle (which has an important role in accommodation) could affect refraction, but no such changes were observed clinically (4-7) after latanoprost application. Thus, ciliary muscle relaxation effect, if present, would be mild and only a part of the mechanism of IOP reduction.

We now focus on the studies investigating the remodeling of the ciliary body ECM. Tamm *et al* (8) studied the changes in the ciliary muscle structure caused by $PGF_{2\alpha}$ in humans and found that the smooth muscle cells lose their connection to the extracellular fibrils because of $PGF_{2\alpha}$-induced lysis of extracellular material. That raised the possibility that PGs might affect the ECM (8). The Weinreb group conducted *in vitro* experiments and reported that the $PGF_{2\alpha}$ acts on the ciliary muscle cells at the AP-1 site and increases the expression of c-FOS (9), and that latanoprost increases the expression of the mRNA (10) and protein (11) of the ECM degrading enzyme, matrix metalloproteinase (MMP), induces an increase in the MMP release by ciliary smooth muscle cells (12), and affects the content of collagen, a major ECM component (13). Similar data was reported by Ocklind, both *in vitro* and *in vivo* (14). Figure 3 shows zymography indicating the changes in the MMP activity when cultured ciliary muscle cells are treated with PG-related solutions. These data strongly suggest that latanoprost affects the ECM remodeling in the ciliary body as summarized in Table 1. However, these changes occurred

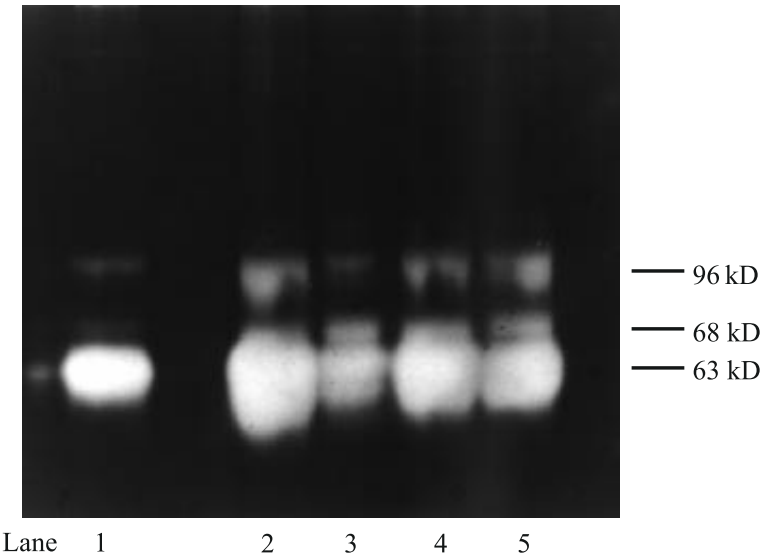


Figure 3. *Effects of PG-related agents on matrix metalloproteinase activity. Substrate zymography shows that PG-related agents (200 mM each) increase MMP activities with 48 hour-exposure. Bands at 97 kD, 98 kD, and 63 kD correspond to MMP-9, MMP-2, and MMP-1 activity, respectively. 17PT-$PGF_{2\alpha}$=17 phenyl-trinor-$PGF_{2\alpha}$, Modified from reference 12.*

Lanes:
1. Vehicle
2. $PGF_{2\alpha}$
3. 17PT-$PGF_{2\alpha}$
4. 11-deoxyl-PGE_1
5. Latanoprost acid

Table 1. *Effects of topical latanoprost on ECM and MMPs in monkey eyes*

Protein	Ciliary Muscle	Iris Root	Sclera adjacent to the ciliary body
collagen type I collagen type III collagen type IV	↓	↓	↓
MMP-1 (collagenase) MMP-2 (gelatinase A) MMP-3 (stromelysin-1)	↑	↑	↑

in the ECM long time after latanoprost treatment and thus cannot explain the significant decrease in the IOP seen clinically 2-3 hour after ophthalmic administration. At present, it may be suggested that both the ciliary muscle relaxation and the ECM changes contribute to the promotion of the aqueous humor outflow.

MECHANISM OF IOP REDUCTION BY UNOPROSTONE

Unoprostone is 13,14-dihydro-15-keto-20-ethyl-$PGF_{2\alpha}$-isopropyl ester developed in Japan. It became available for clinical use in 1994 in Japan, and in 2001 in North America. As indicated in Figure 1, it has a ketone group at position 15 and has very low selectivity toward any of the known PG-receptors (15). Furthermore, unoprostone is rapidly metabolized in the eye after ophthalmic administration (16). Figure 4 shows the intraocular metabolism of latanoprost and unoprostone. The major pharmacologically active component in the eye is not unoprostone but rather is likely to be its metabolite(s)(Fig. 5). However, the metabolites have PG receptor affinities that are even lower than unoprostone itself (personal communication). Therefore, it seems unlikely that the mechanism of action of this drug is through pharmacological effects on the previously reported PG receptors.

The mechanism of IOP reduction by unoprostone has been proposed to be either promotion of aqueous humor through the conventional route (17) or an increase in the uveoscleral outflow, but there is no agreement regarding this issue. As with latanoprost, unoprostone has been reported to increase the MMP activity in *in vitro* experiments (Fig. 6)(18), but it remains unclear why the PG receptor affinity is extremely low even though the drug has pharmacological activity. As seen for latanoprost (19), the intraocular unoprostone metabolite(s) can induce endogenous $PGF_{2\alpha}$ and PGE_2 (Fig. 7)(20), and the induction of endogenous PGs may contribute to the drug activity. However, the details of the mechanisms of IOP reduction by unoprostone remain unclear.

MECHANISM OF IOP REDUCTION BY BIMATOPROST

Bimatoprost, which is (Z)-7-[(1R, 2R, 3R, 5S)-3, 5-dihydroxy-2-[(1E, 3S)-3-hydroxy-5-phenyl-1-pentenyl] cyclopentyl]-5-N-ethyl heptenamide, has a chemical structure (Fig. 1) similar to the $PGF_{2\alpha}$ analogues. The free acid of bimatoprost is identical to that of latanoprost with the exception of a double bond instead of single bond at the carbon 13-14 position. A recent study has demonstrated binding of bimatoprost to the FP prostanoid receptor. The free acid of bimatoprost is known to be a potent FP receptor agonist.

Bimatoprost enhances the pressure-sensitive outflow pathway. There is a report of additional beneficial effects that may include an increase in the rate of flow in the uveoscleral outflow pathway and lowering of the episcleral venous pressure (21), but the detailed mechanisms are unknown.

MECHANISM OF IOP REDUCTION BY TRAVOPROST

Travoprost (AL-6221), which is isopropyl (Z)-7-[(1R, 2R, 3R, 5S)-3, 5-dihydroxy- 2-[(1E, 3R)-3-hydroxy-4-[(α, α, α-trifluoro-m-tolyl)oxy]-1-butenyl]cyclopentyl]-5-heptenoate, is the isopropyl ester of a single enantiomer of the selective FP prostaglandin receptor agonist, fluprostenol. It is a PG analogue with a high FP receptor selectivity (22) and promotes aqueous humor outflow *via* the uveoscleral route (23). Its ability to decrease the IOP seem to be better than timolol and equivalent to latanoprost. Only a few adverse effects are known. However, a detailed mechanism of reduction in the IOP has not been elucidated.

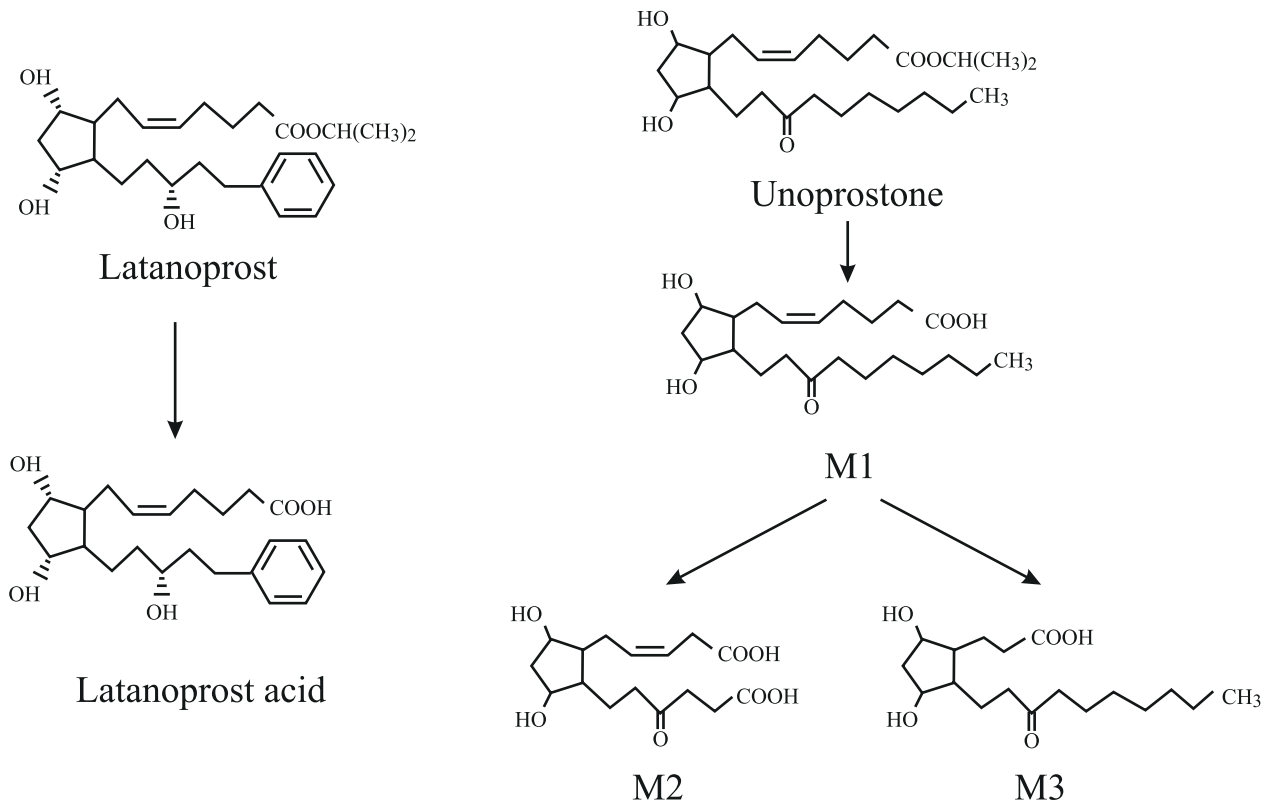


Figure 4. *Intraocular metabolism of latanoprost and unoprostone.*

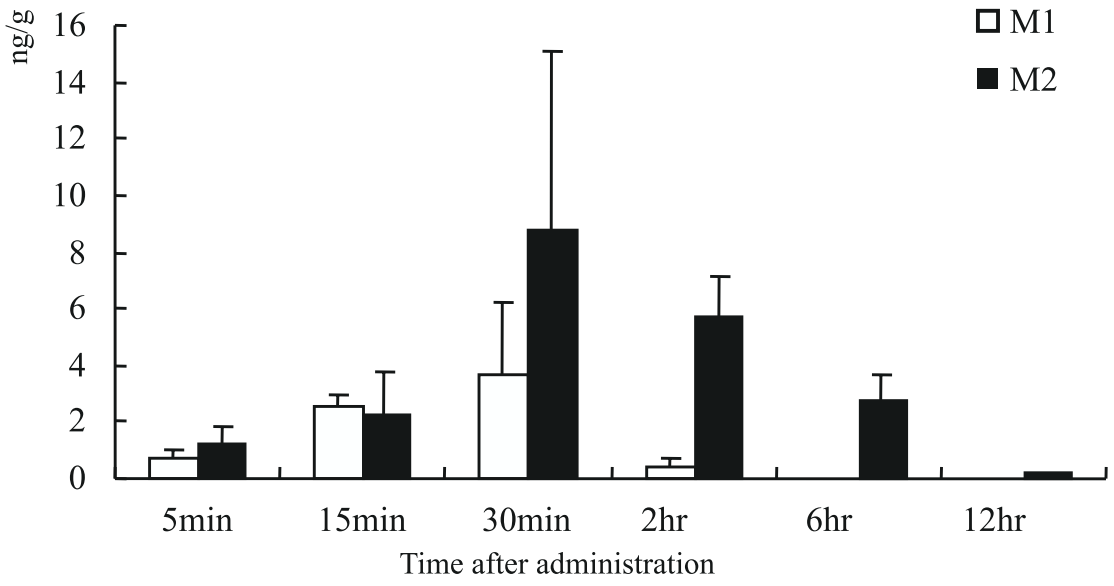
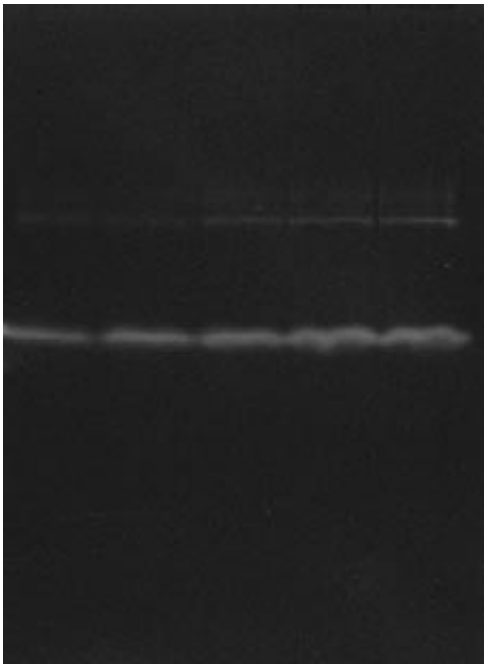


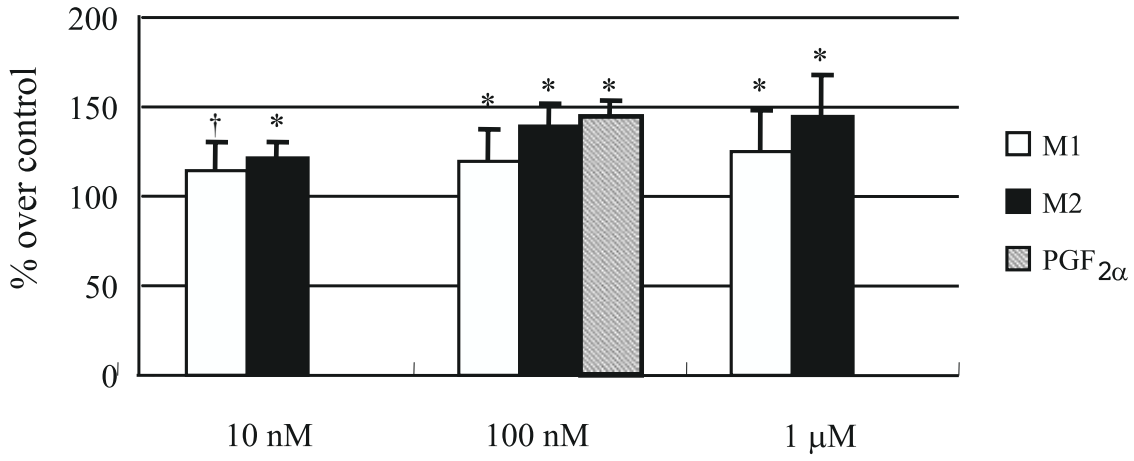
Figure 5. *Concentrations of unoprostone ant its metabolites (M1 and M2) in the anterior chamber.*
Note that no unoprostone but only M1 and M2 are detected in the anterior chamber when a single drop of radioisotope-labeled unoprostone was administered to rabbit eyes. Bar, standard deviation, n = 4. Modified from reference 16.

Figure 6. *Effects of unoprostone metabolites on matrix metalloproteinase acitivity.*



(a) *A representative result of substrate zymography. M1 and M2 increase MMP-2 and 9 activities compared with vehicle control.*

Lanes:
1. Vehicle
2. 10 nM M1
3. 10 nM M2
4. 10 μM M1
5. 10 μM M2



(b) *Changes of MMP-2 activity in a medium from ciliary muscle cells. Y axis represents % of MMP-2 activity over the vehicle control, * $p < 0.05$, † $p = 0.06$,* versus *control; bar, standard deviation, n = 5. Modified from reference 18.*

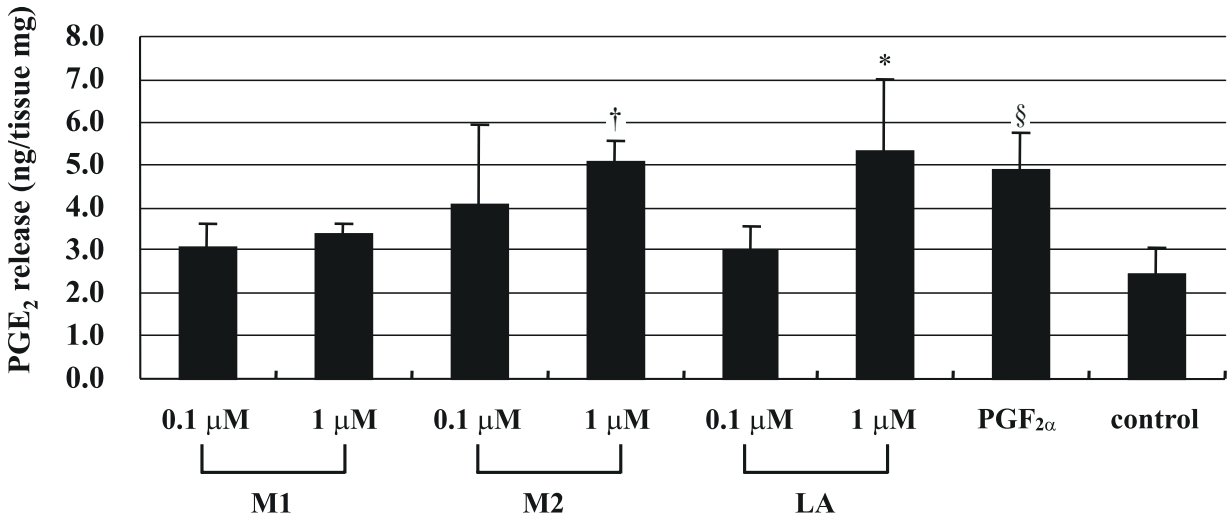


Figure 7. *Effects of latanoprost and unoprostone on the release of endogenous PGE_2 from isolated iris tissue. All examined compounds increased the release of endogenous PGE_2 compared with the control. 1 μM M2, latanoprost, and $PGF_{2\alpha}$ significantly induce the release of PGE_2 by isolated iris tissue. Each experiment was performed in duplicate (n= 4). * p = 0.02, † p = 0.03, § p < 0.05* versus *control, ANOVA followed by post-hoc. LA, acid of latanoprost; bar, SEM.*

ADVERSE EFFECTS CAUSED BY PG-RELATED AGENTS

Increased pigmentation of the iris

A frequently seen adverse effect of the currently available PG-related solutions is the increased pigmentation of the iris (24-27). Figure 8 shows representative iridial pigmentation induced by either latanoprost or unoprostone. The mechanism of pigment deposition by latanoprost involves increase of the tyrosinase activity without inducing cell division in the iris or dermal melanocytes, and thus causing melanin increase (Fig. 9)(27-34). Our results showed that in addition to the increased melanogenesis by increased tyrosinase activity, latanoprost but also causes an increased pigmentation of melanin (28,29). We and others reported an increase in eumelanin/pheomelanin ratio in the latanoprost-administered animal models (28,29,35). We have observed the same effect also for unoprostone, but with a lower incidence of the increased pigmentation compared to latanoprost (28). Other PG-related agents have also been reported to increase the pigmentation of the iris, but the details remain unclear. The increased melanin is not released outside of the cell, and there is no increase in the melanin deposition in the iridocorneal angle and other ocular tissues. IOP elevation or a malignant transformation have not been observed. Thus, at this point, this complication remains only an esthetic problem.

Hair-growth

Recently, latanoprost has been recognized as a drug capable of regularly inducing hypertrichosis involving eyelashes, adjacent adnexal hair, and vellus hair of the skin (36,37). Hair growth cycle involves the anagen, catagen, and telogen, and latanoprost has been suggested to cause longer anagen follicle phase than normal compared to the telogen follicle phase (38). This effect is said to be reversible, but this has not been confirmed. Hair growth involves many genes and growth factors that affect the hair growth and hair cycling, and how latanoprost is implicated remains unclear.

Recurrence of uveitis

There have been reports of uveitis recurring in patients with a history of uveitis treated with latanoprost. The mechanism is not well understood. Latanoprost has been reported to induce PGE_2, an PG involved in inflammation (20), which may be involved in this phenomenon.

Cystoid macular edema (CME)

CME is an important local adverse effect seen in PG-related solutions because it affects vision. CME is thought to be more frequent in patients with a history of intraocular surgery, where the blood/aqueous humor barrier has been affected. Figure 10 shows a representative case with cystoid macular edema induced by latanoprost ophthalmic solution. The details of the pathogenetic mechanism is unclear, but the involvement of endogenous PGE_2 has been proposed, because latanoprost induces endogenous PGE_2 (20), and because concurrent administration of non-steroidal anti-inflammatory drugs with

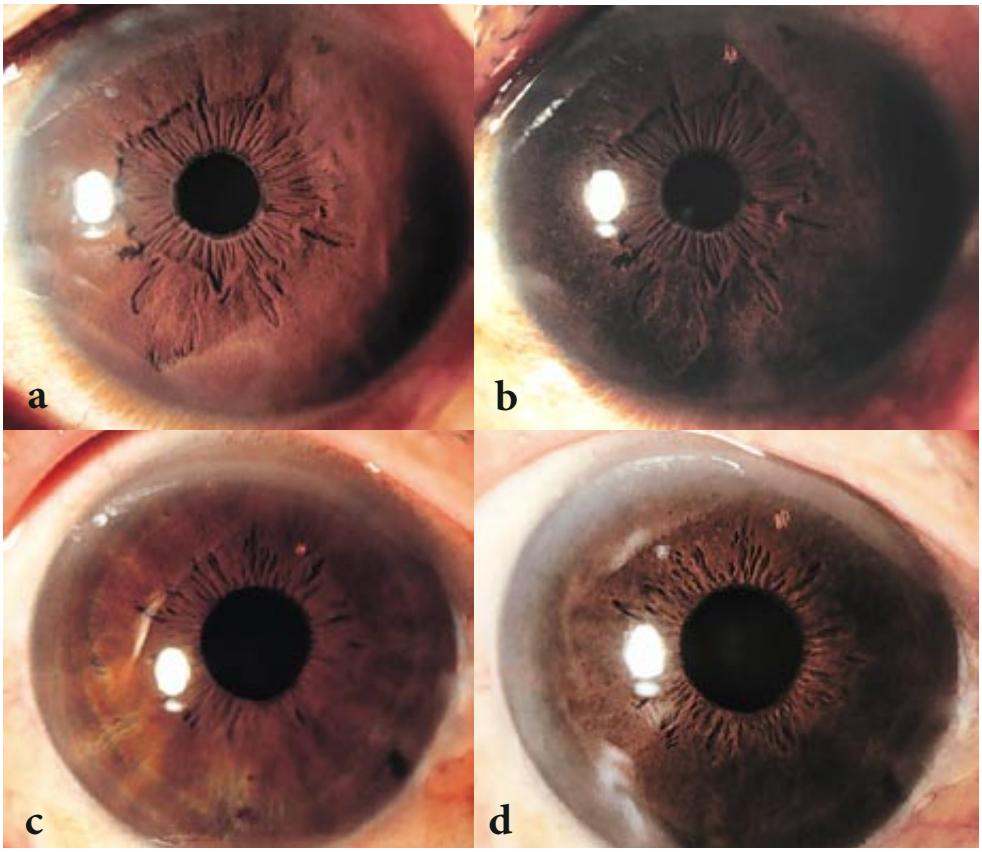


Figure 8. *Representative cases of PG-induced iridial pigmentation. Before treatment of PG-related ophthalmic solution, iridial pigmentation was normal* ***(a, c)****. After initiation of PG-related ophthalmic solution, scattered pigmentation was observed and iridial pigmentation was gradually increased (****b****, latanoprost;* ***d****, unoprostone). The pattern of increased pigmentation by unoprostone was similar to that by latanoprost.*

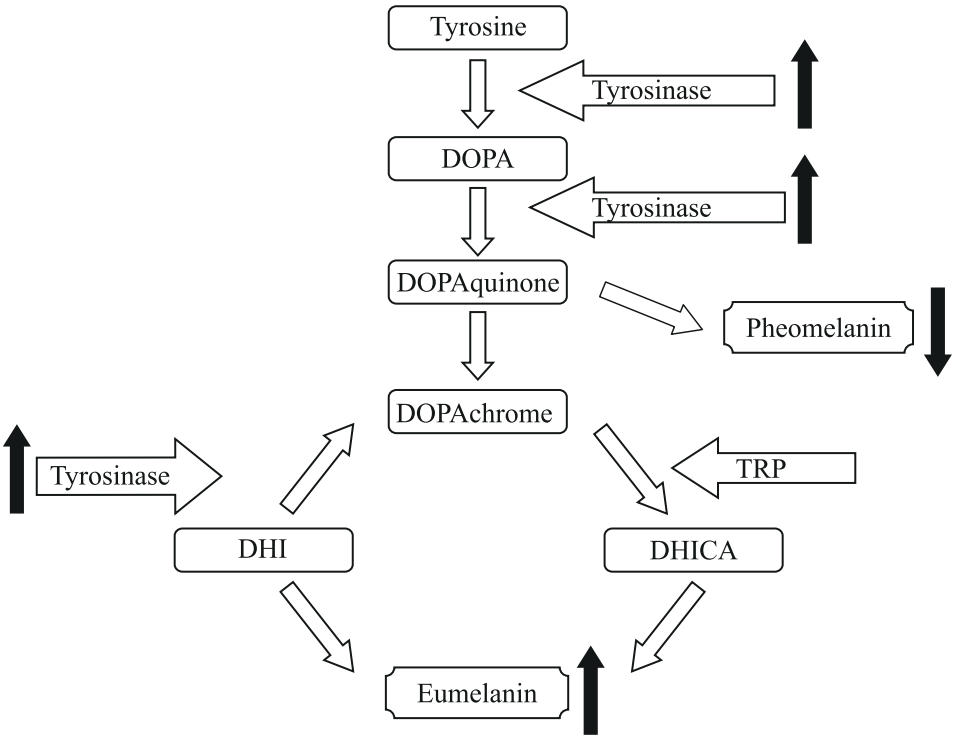


Figure 9. *A schematic diagram of melanogenic pathway. PG-related ophthalmic solutions could increase tyrosinase activity and influence the nature of melanin converting normal melanogenesis in iridial pigmentation. DOPA, 3,4-dihydroxyphenylalanine; TRP, tyrosinase-related protein; DHI, 5,6-dihydroxyindole; DHICA, 5,6-dihydroxyindole-2-carboxylic acid.*

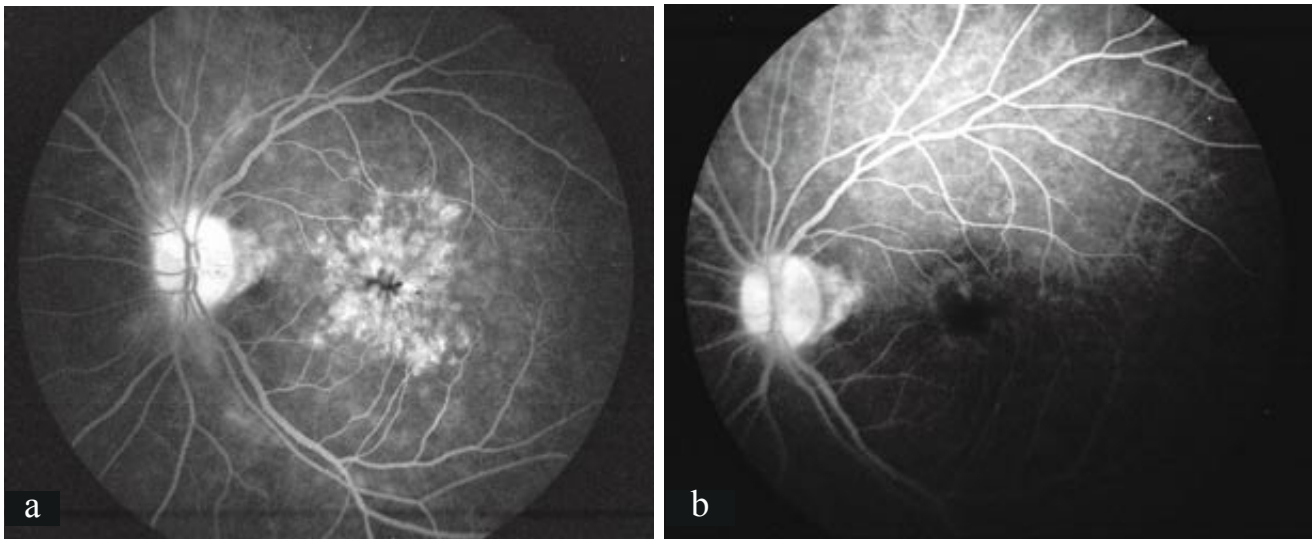


Figure 10. *A representative case with cystoid macular edema induced by latanoprost ophthalmic solution.*
(a) *The late phase fluorescein angiography (FAG) shows a 1.5 disc diameter of cystoid macular edema (CME) observed 2 months after the initiation of treatment with latanoprost ophthalmic solution. The visual acuity was 20/30.*
(b) *The late phase FAG shows disappearance of CME after the discontinuation of latanoprost. The visual acuity was 20/20.*

latanoprost after cataract surgery suppresses the development of CME (39). This adverse effect is rare in patients with no history of breakdown of the blood/aqueous humor barrier (40), and it is therefore considered that the administration of latanoprost should be performed with caution in patients with a history of barrier breakdown. CME has not been reported with unoprostone, probably because of the rapid intraocular metabolism of unoprostone and its conversion into inactive compound(s)(16). There are no data concerning the development of this adverse effect in the other two PG-related solutions because of the short time elapsed after their approval.

CONCLUSION

The pharmacological action of the PG-related agents is predominantly to promote the uveoscleral outflow of aqueous humor. Their introduction has increased the interest in the uveoscleral outflow, which previously had not received much attention. At the same time, many questions remain unanswered. It is widely recognized that uveoscleral outflow in the physiological state accounts for only 10% of the aqueous humor outflow, and it remains unclear how the PG-related solutions can then cause a remarkable IOP decrease. The conventional route is directly in contact with the veins and thus is affected by the venous pressure, while the uveoscleral route is not directly connected to the vasculature and is not affected by the venous pressure. Thus, the uveoscleral route may reduce the IOP more effectively than the conventional route, because its use is not limited by the effects of the venous pressure. Therefore, the approach involving the uveoscleral outflow has attracted new attention in the treatment of glaucoma.

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