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Update on the Mechanism of Action of Topical Prostaglandins for Intraocular Pressure Reduction

Carol B. Toris, PhD[1], **B'Ann T. Gabelt, MS**[2], and **Paul L. Kaufman, MD**[2]

[1]Department of Ophthalmology and Visual Sciences, University of Nebraska Medical Center, Omaha, Nebraska, USA

[2]Department of Ophthalmology and Visual Sciences, University of Wisconsin, Madison, Wisconsin, USA

Abstract

A decade has passed since the first topical prostaglandin analog was prescribed to reduce intraocular pressure (IOP) for the treatment of glaucoma. Now four prostaglandin analogs are available for clinical use around the world and more are in development. The three most efficacious of these drugs are latanoprost, travoprost, and bimatoprost, and their effects on IOP and aqueous humor dynamics are similar. A consistent finding is a substantial increase in uveoscleral outflow and a less consistent finding is an increase in trabecular outflow facility. Aqueous flow appears to be slightly stimulated as well. Prostaglandin receptors and their associated mRNAs have been located in the trabecular meshwork, ciliary muscle, and sclera providing evidence that endogenous prostaglandins have a functional role in aqueous humor drainage. Earlier evidence found that topical PG analogs release endogenous prostaglandins. One well-studied mechanism for the enhancement of outflow by prostaglandins is the regulation of matrix metalloproteinases and remodeling of extracellular matrix. Other proposed mechanisms include widening of the connective tissue-filled spaces and changes in the shape of cells. All of these mechanisms alter the permeability of tissues of the outflow pathways leading to changes in outflow resistance and/or outflow rates. This review summarizes recent (since 2000) animal and clinical studies of the effects of topical prostaglandin analogs on aqueous humor dynamics and recent cellular and molecular studies designed to clarify the outflow effects.

Keywords

aqueous humor; intraocular pressure; matrix metalloproteinases; prostaglandin; trabecular outflow; uveoscleral outflow

Introduction

All of the clinically available drugs for the treatment of elevated intraocular pressure (IOP) have direct effects on one or more parameters of aqueous humor dynamics. IOP usually is

Correspondence: Carol B. Toris, Ph.D., Department of Ophthalmology, 985840 Nebraska Medical Center, Omaha, NE 68198-5840. Telephone: (402) 559-7492, Fax: (402) 559-5368, E-mail address: ctoris@unmc.edu.
Reprint address: Carol B. Toris, PhD, Department of Ophthalmology, 985840 Nebraska Medical Center, Omaha, NE 68198-5840. E-mail address: ctoris@unmc.edu

reduced by slowing the production rate of aqueous humor, by decreasing the resistance to flow through the trabecular meshwork, by increasing drainage through the uveoscleral outflow pathway, or by a combination of these mechanisms. Currently, the most effective outflow drugs approved for clinical use are prostaglandin (PG) $F_{2\alpha}$ analogs. These drugs reduce IOP by stimulation of aqueous humor drainage primarily through the uveoscleral outflow pathway but significant effects on trabecular outflow facility also have been reported.[67, 85] Three $PGF_{2\alpha}$ analogs (bimatoprost, latanoprost, and travoprost) are approved for glaucoma therapy in the USA, one additional analog (unoprostone) is prescribed in Japan and a new analog (tafluprost) is in clinical trials in Japan. Travoprost and latanoprost are ester prodrugs of $PGF_{2\alpha}$. Bimatoprost is the amide prodrug of 17-phenyl-$PGF_{2\alpha}$86 and has been classified by some as a prostamide, [86] although this classification has been somewhat controversial.[7, 37, 56, 57, 58, 86, 87] Unoprostone is an analog of a pulmonary metabolite of $PGF_{2\alpha}$ and sometimes labeled a docosanoid. [26] Tafluprost is a difluoroprostaglandin derivative of $PGF_{2\alpha}$. [62] Agonists of DP, EP, and TP receptors have been or are being investigated in animal models for their IOP efficacy and potential as new glaucoma therapeutic drugs. None of these agonists has yet to be approved for clinical use.

This review summarizes recent (since 2000) animal and clinical English-language studies of the effects of topical PG agonists on aqueous humor dynamics and recent cellular and molecular studies designed to clarify the outflow effects.

Aqueous Humor Dynamics (Table 1)

Latanoprost, travoprost, and bimatoprost produce similar increases in uveoscleral outflow of several-fold. Increases in trabecular outflow facility also have been reported but this finding has not been found consistently (Table 1). Unoprostone, the least efficacious of the four compounds, appears to have little effect on uveoscleral outflow in humans. Rather it works mainly by increasing trabecular outflow facility. [69] The new fluoroprostaglandin $F_{2\alpha}$, tafluprost, increases uveoscleral outflow and aqueous flow in monkeys [62] but has yet to be studied in humans. Earlier studies[13, 90] have reported that the topical PG analogs release endogenous prostaglandins that may contribute to the observed ocular hypotensive effects. Tafluprost in mice reportedly works in part through FP receptor-mediated prostaglandin production acting through the prostanoid EP_3 receptor. [49] Studies published between 2000 and 2008 of FP, DP, and EP receptor agonists and their effects on aqueous humor dynamics in humans and nonhuman primates are summarized in Table 1. Studies predating 2000 are found in an earlier review. [67]

TRABECULAR OUTFLOW FACILITY

Trabecular outflow facility is not always increased following topical treatment with PG analogs but evidence is building that the effect is real and not unique to any one drug of this class. Latanoprost, travoprost, bimatoprost, and unoprostone all have been found to significantly increase trabecular outflow facility in at least one clinical study (Table 1).

Compared to humans, the trabecular meshwork of monkeys seems to be less affected by PG analogs. Trabecular outflow facility was unchanged following multiple topical treatments of monkeys with $PGF_{2\alpha}$-isopropyl ester, [22] tafluprost, [62] and travoprost, [71] the DP receptor agonist AL-6598, [72] and EP receptor agonists butaprost [44] and 8-iso PGE_2 23 (Table 1). Exceptions do exist. One drop of 17-phenyl trinor 8-iso PGE_2 and the selective EP_4 receptor agonist, 3,7-dithia PGE_1 increased outflow facility sufficiently in normotensive monkey eyes to account for most, if not all of the IOP reduction [88] (Table 1). An older study found an increase in outflow facility at 4 hours after one topical drop of $PGF_{2\alpha}$. [35]

One potential reason for the apparent differences in trabecular outflow facility effect among the various PG agonists is the method of measurement. Two noninvasive methods, tonography and fluorophotometry, and two invasive methods, two-level constant pressure perfusion, and isotope accumulation, are used to make the assessment. All methods measure trabecular outflow facility, but confounding factors are known to exist, including ocular rigidity (a measure of eye stiffness), pseudofacility (the facility of flow of aqueous humor from the posterior to anterior chamber resulting from the probe-induced increase in IOP), and uveoscleral outflow facility. The name of the measured variable *trabecular outflow facility* is not entirely accurate because of the inclusion of these other factors in the various measurements. All of the measurement techniques assume that uveoscleral outflow facility is very small and affected little by the measurement itself. This assumption is based on monkey studies[8, 68] reporting that uveoscleral outflow is relatively pressure-independent. However, if an experimental manipulation were to increase uveoscleral outflow facility, this could be interpreted erroneously, as an increase in trabecular outflow facility. It is thought by some that PGs increase uveoscleral outflow facility but this has yet to be proven experimentally. These methods may not detect changes in trabecular outflow facility if the changes are overshadowed by strong effects on uveoscleral outflow and/or uveoscleral outflow facility.

The length of time of treatment could be another factor contributing to the differing effects of PGs on trabecular outflow facility. The immediate IOP effects that occur from a single dose of a PG analog may be mediated by cellular mechanisms different from those that occur after repeated applications or continuous exposure.[9, 83, 91] Therefore, findings from multiple doses of each PG should be compared before concluding that one PG analog acts through mechanisms different from all others.

Mice are being used with increasing frequency to evaluate aqueous humor dynamics because of their potential for genetic manipulation in addition to their ocular similarities to humans. These animals exhibit increases in outflow facility 2 hours after one 4-μl drop of latanoprost.[18] Several limitations to using this animal model should be mentioned. The size of the eye makes accurate measurement difficult. Inflow and outflow are very slow (many-fold slower than in humans),[1] and changes in flow can be near the limit of detection. Additionally, the anesthesia needed for most measurements quickly and profoundly affects IOP.[31] IOPs vary among strains of mice,[30] and aqueous humor outflow rates may vary among strains as well. Further research is needed to characterize differences in aqueous humor dynamics among the murine strains.

UVEOSCLERAL OUTFLOW

Increases in uveoscleral outflow have been reported with topical treatment of bimatoprost and latanoprost in ocular normotensive and hypertensive subjects (Table 1).[11, 16, 20, 73] Travoprost increased uveoscleral outflow in monkeys[71] and marginally increased it in ocular hypertensive patients as well.[70] Unoprostone, the weakest of the four prescribed PG analogs, is the only one that did not affect uveoscleral outflow in humans despite 5 days of twice-daily dosing.[69]

Multiple topical drops of agonists for FP receptors (tafluprost[62]), DP receptors (AL-6598[72]), and EP_2 receptors (butaprost[44] and 8-iso PGE_2 78) increased uveoscleral outflow in monkeys (Table 1). In contrast, one drop of the EP_4 agonist, 3,7-dithia PGE_1, had no effect on uveoscleral outflow in monkeys[88]. A multiple dose study is needed to clarify whether the effect persists with repeat dosing.

AQUEOUS FLOW

Most studies investigating aqueous flow have found that PG analogs produce a small (10–15%) increase that may or may not be statistically significant and is not clinically important. A

significant increase in aqueous flow was found at night in young healthy Japanese volunteers treated with latanoprost, [41] and during the day and at night in healthy predominantly Caucasian volunteers treated with bimatoprost. [11] Additionally aqueous flow increased during the day in monkeys treated with a DP agonist. [72] This effect does not contribute to any reduction in IOP but an increase in aqueous flow could be considered a healthy side-effect of topical PG analogs because aqueous humor carries essential nutrients and removes waste products, crucial for keeping the avascular tissues of the anterior segment healthy.

EPISCLERAL VENOUS PRESSURE

Three studies have reported no change in episcleral venous pressure in patients with ocular hypertension treated for one week with latanoprost, travoprost, or unoprostone (Table 1). The measurements, (made with a commercially available episcleral venomanometer, EyeTech, Morton Grove, IL), are difficult to make with accuracy and consistency. Nevertheless, because no study found any trend to suggest a change, it seems reasonable to conclude that the PG effect on episcleral venous pressure is minimal.

Cellular and Molecular Studies (Table 2)

TRABECULAR MESHWORK

Organ-cultured anterior segments and trabecular meshwork cell cultures provide strong evidence that PG analogs can alter the resistance in trabecular outflow. PGs have direct effects on matrix metalloproteinases (MMPs), neutral proteases that initiate degradation of the extracellular matrix and play a major role in regulating resistance to flow through tissues. MMPs are expressed by human trabecular meshwork [2] and directly control outflow resistance in human organ-cultured anterior segments. [9] The activity of MMPs is regulated by tissue inhibitors of metalloproteinases (TIMPs). [10] Currently four TIMPS (TIMP-1, -2, -3, -4) have been identified in mammals and each TIMP targets specific MMPs. [42] In one study, [47] cultures of human trabecular meshwork cells treated with latanoprost acid for 24 hours had increased expression of MMPs -1, -3, -17 and -24 and TIMPs -2,-3, and -4. A study [6] of human organ-cultured anterior segments infused with latanoprost acid found increased outflow facility at 24 hours after administration when compared to control anterior segments (67% versus 6%) but no changes in the amount of MMPs or scleral hydraulic conductivity. [6] Histological examination found regions of focal detachment and loss of Schlemm's canal endothelial cells and extracellular matrix in some areas of the trabecular meshwork. [6] The focal cell loss was reasoned to be due to cytoskeletal and focal adhesion changes, [6] since PGs in aortic smooth muscle cells cause disassembly of actin stress fibers and inhibition of phosphorylation of paxillin and other focal adhesion proteins. [12]

Bimatoprost increases outflow facility by 40% in human organ-cultured anterior segments within 48 hours of treatment. This effect was blocked by preincubation with AGN 211334, thought to be a prostamide-selective antagonist, [76] or , alternatively, an inhibitor of bimatoprost hydrolysis. [7] Similarly, pig organ-cultured anterior segments perfused at a constant pressure of 15 mmHg, showed increased outflow by up to 62% at 8 hours after topical administration of bimatoprost and by 30% at 5 hours after intracameral administration of $PGF_{2\alpha}$. [74] Human trabecular meshwork monolayer cultures [6] treated with bimatoprost had a 78% increase in hydraulic conductivity which also was blocked by AGN211334. [76]

PGE_1 increases outflow facility by 26% in human organ-cultured anterior segments. [19] This effect probably occurs by an adenylyl cyclase-dependent pathway activated primarily by the predominant EP_2 receptors in the trabecular meshwork. [32] Stimulation of EP_2 receptors in trabecular meshwork is coupled to the activation of high-conductance Ca^{+2}-activated K^+ channels (BK) which may contribute to the relaxant activity of EP_2 agonists in isolated

trabecular meshwork strips. [61] However, outflow facility was not stimulated and cAMP production was not altered after short exposure periods with $PGF_{2\alpha}$ or placebo in human organ-cultured anterior segments. [19]

Prostaglandin receptors have been identified in human trabecular meshwork tissue but a prostamide receptor has not yet been cloned. The genes for all prostanoid receptors are expressed in human trabecular meshwork. Gene expression for the EP_2 receptor is most abundant, followed by FP, TP, IP and EP_4, with DP and EP3 at the lowest levels. [32] Immunofluorescent labeling of FP and EP pαostanoid receptor subtypes in normal human trabecular meshwork tissue showed positive staining for EP_1 on trabecular cells of the outer portion of the meshwork and cells lining Schlemm's canal. EP_2 was localized to the outer wall and periphery of Schlemm's canal. EP_3 and EP_4 labeling was present on trabecular cells along the entire meshwork. Moderate expression of FP receptor protein was present in the outer portion of the trabecular meshwork and endothelial cells of Schlemm's canal, collector channels and aqueous veins. [55]

Human trabecular meshwork cells in culture express many of the same PG receptors as are found in intact tissue. Cultured trabecular meshwork cells can produce PGE_2 and low levels of $PGF_{2\alpha}$.[83, 84] Additionally, FP receptors have been identified in human trabecular meshwork cells as determined by the presence of mRNA, protein, and a functional response (increased inositol phosphate accumulation and intracellular calcium release) to $PGF_{2\alpha}$5 and numerous synthetic FP-selective PG agonists. [58] PGE_2 elicits its biological effects via four G-protein-coupled receptor subtypes which stimulate phosphoinositide turnover with elevation in intracellular-free calcium (EP_1 and some EP_3), activation of adenylyl cyclase and elevation of intracellular cAMP (EP_2 and EP_4) or inhibition of adenylyl cyclase (EP_3).[17, 43] Prolonged treatment of human trabecular meshwork cells with latanoprost or $PGF_{2\alpha}$ ethanolamide causes an increase in expression of genes for insulin-like growth factor-1 (IGF-1) and fibroleukin that could act to increase outflow facility. IGF-1 is reported to increase the level of MMPs, stromelysin and gelatinase in trabecular meshwork cells. The protease activity of fibroleukin may be active against a component in the extracellular matrix. [91]

Unoprostone free acid (UF-021) shows low affinity for all prostanoid receptors and weak functional responses via FP receptor activation. [57] Several molecular events have been associated with unoprostone exposure. A reduction in the activity of L-type Ca^{2+} channels via a signal transduction pathway was mediated by tyrosine kinases. [65] Activation of BK channels by unoprostone free acid inhibited trabecular meshwork contraction leading to an increase in outflow. [66]

Endothelin-1 is involved in regulating the contractility of the trabecular meshwork. FP receptor agonists can block endothelin-1 induced contractility of the trabecular meshwork. Evidence indicates this inhibition is mediated by the FP receptor. [64]

UVEOSCLERAL TISSUES

Immunohistochemistry studies of EP and FP receptor localization in the uveoscleral tissue in normal human donor eyes indicate the presence of EP-1, -2, -3, -4 and FP receptors in the ciliary body and sclera. FP receptors are most abundant in the circular portion of the ciliary muscle. [55]

Several mechanisms have been proposed to explain the PG-induced increase in uveoscleral outflow: remodeling of the extracellular matrix of the ciliary muscle,[45, 53, 80] and sclera[33, 82] (Molik et al, unpublished data, abstract 406 presented at the 2006 ARVO annual meeting) causing changes in the permeability of these tissues, widening of the connective tissue-filled spaces among the ciliary muscle bundles,[39, 63] which may be caused in part by relaxation of

the ciliary muscle,[51, 75] and changes in the shape of ciliary muscle cells as a result of alterations in actin and vinculin localization within the cells. [60]

Ciliary muscle relaxation has been suggested as responsible for the initial reduction in IOP from topical PGs. This does not appear to be the case for all PGs and their agonists. PGE_1 and PGE_2 relaxed isolated monkey ciliary muscle strips precontracted with carbachol [89] but 3,7-dithia PGE_1 88, $PGF_{2\alpha}$ and latanoprost did not. [89]

Remodeling of the extracellular matrix within the ciliary muscle and sclera is the most thoroughly understood effect of PG treatment. Dissolution of collagen types I and III within the connective tissue-filled spaces between the outer longitudinally oriented muscle bundles[39, 63] results from PG-stimulated induction of enzymes MMP1, 2, and 3 in the ciliary muscle and surrounding sclera. [25] Long-term (1 year) unilateral treatment of monkey eyes with topical bimatoprost, latanoprost, sulprostone (EP_3/EP_1 agonist) or AH13205 and butaprost (EP_2 agonists) found that in all cases the tissue spaces of the ciliary muscle were enlarged and organized into elongated tube-like spaces, covered by endothelial-like cells often in contact with the basement membrane, and contained myelinated nerve fiber bundles.[44, 52] These fluid pathways resembled a kind of lymphatic system described in the choroid. [34] Changes in the trabecular meshwork also were present. MMP expression in human ciliary body tissue and ciliary muscle cells was determined after latanoprost acid treatment for 24 hours. The mRNA of MMP-1,-2, -3, -11, -12, -14, -15, -16, -17, -19, and -24 as well as TIMP-1 to -4 were found in ciliary body tissue and ciliary muscle cells. Latanoprost increased MMP-3,-9, -17, and TIMP-3 and down-regulated MMP-1, -2, -12, -14, -15, and -16 and TIMP-4. [46] Latanoprost acid induced a concentration-dependent increase in MMP-1, -3, and -9 gene transcription [81] and a concentration - and time-dependent increase in TIMP-1 but not TIMP-2 mRNA and protein. [4]

Loss of cyclooxygenase (COX)-2 expression in the ciliary body of humans has been associated with glaucoma. [40] This association has led to studies investigating the connection between PGs, COX-2 expression and MMPs. Indeed, the IOP-lowering action of latanoprost appears to be associated with induction of COX-2 and subsequent MMP-1 expression in human nonpigmented epithelial cells. [27] MMP-1 released into the aqueous humor would be expected to flow into the ciliary muscle and through the trabecular meshwork and Schlemm's canal to potentially increase outflow via multiple routes.

Studies to elucidate additional cellular mechanisms associated with PG-induced MMP secretion are ongoing. $PGF_{2\alpha}$- and latanoprost-induced secretion and activation of MMP-2 in ciliary muscle cells were shown to occur via protein kinase C and extracellular signal regulated protein kinase 1/2-dependent pathways. [28] Mitogen-activated protein kinase activity was stimulated in human ciliary muscle cells with travoprost acid>PGF2α> latanoprost acid> bimatoprost > latanoprost = bimatoprost acid. The FP antagonist AL-8810 completely inhibited the mitogen-activated protein kinase activity induced by bimatoprost and bimatoprost acid, indicating that both agonists were activating the FP receptor. [57]

Inhibition of the latanoprost-induced reduction of IOP in rats by thalidomide suggested that the IOP-lowering response is mediated, in part, through tumor necrosis factor-α-dependent signaling pathways. Treatment of human ciliary muscle cells with tumor necrosis factor-α increased the secretion of MMP-1, and -2 (Husain et al., unpublished data, abstract 219 presented at the 2006 ARVO annual meeting).

$PGF_{2\alpha}$ can stimulate the formation of endogenous PGs by stimulation of phospholipase A2 and release of arachidonic acid for PG synthesis. [90] Human ciliary muscle cells exposed to $PGF_{2\alpha}$ ethanolamide or latanoprost for 9 days show a downregulation of the FP receptor. In

the same study, downregulation of the aquaporin-1 and versican genes are proposed to increase flow through the ciliary muscle and decrease IOP. [91]

PG-induced changes in the sclera also are important in the regulation of uveoscleral outflow and may be used to enhance transscleral delivery of peptides and other high-molecular-weight substances to the posterior segment of the eye. Five days of topical treatment with $PGF_{2\alpha}$-isopropyl ester increased MMP-1, -2, and -3 in the sclera of monkeys. [79] Immunocytochemistry studies and mRNA analysis of human sclera and cultured human scleral fibroblasts showed the presence of EP_1, EP_2 and FP receptor subtypes but not EP_3 and EP_4 subtypes. [3] Human scleral permeability to dextrans was measured in an Ussing chamber following exposure to $PGF_{2\alpha}$ and latanoprost acid for 1–3 days. Scleral permeability increased in a dose- and time-dependent manner. This was accompanied by an increase in MMP concentration in the media with the greatest increases in MMP-2 and -3 compared to MMP-1. [33] $PGF_{2\alpha}$ and latanoprost acid also induced increases in mRNA for MMPs and TIMPs in human scleral organ cultures. [82] X-ray diffraction analysis of human scleral explants showed that incubation in $PGF_{2\alpha}$-containing media caused the collagen helix to undergo gelatinization similar to what was found after incubation with MMP-enriched media (Molik et al, unpublished data, abstract 406 presented at the 2006 ARVO annual meeting).

GENETIC STUDIES

Mice deficient in various PG receptors have been used to determine the role of prostanoid receptor subtypes in mediating the IOP-lowering response to clinical PG analogs. Studies in FP receptor-deficient mice have shown that the FP receptor is essential for the early IOP-lowering response to topical latanoprost, travoprost, bimatoprost, and unoprostone. [48] The involvement of the FP receptor in the IOP reduction with long-term dosing is unknown. Upregulation of MMP-2, -3, -9 and FP mRNA in the sclera following 7 days of topical treatment with latanoprost also was dependent on an intact FP receptor gene (Crowston et al, unpublished data, abstract 1551 presented at the 2007 ARVO annual meeting). EP receptor-deficient mice have been studied in similar ways. When EP_1, EP_2, and EP_3 receptor-deficient mice and their wild-type background strain were treated topically with latanoprost, travoprost, bimatoprost, or unoprostone, it was found that EP_3 receptors were involved in the IOP- lowering response to latanoprost, travoprost, and bimatoprost at 3 hours after drug administration but EP_1 and EP_2 receptors are not. [50]

PHARMACOLOGIC DIFFERENCES AMONG THE PROSTAGLANDINS

Natural prostaglandins ($PGF_{2\alpha}$, PGE_2, PGD_2, PGI_2) have the highest affinity for their respective receptors (FP, EP, DP, IP) but are relatively nonselective for these and other PG receptors (TP) and their subtypes (DP_1, DP_2, $EP_{1–4}$) in receptor-binding studies. [57] Prostamides are also naturally occurring neutral lipids which have very little activity at prostaglandin receptors but, thus far, only pharmacologic evidences exists for a prostamide receptor. [87] The therapeutic derivatives of $PGF_{2\alpha}$, either amide or ester prodrugs, are powerful ocular hypotensive drugs and either mediate their effects primarily via FP receptor activation or potentially via some yet unidentified receptor activation. [57]

It has been reported that the prostamide bimatoprost stimulates neither FP nor EP_2 receptors and its effects on aqueous humor outflow, although similar to latanoprost and travoprost, are accomplished via a receptor distinct from these pure FP receptor agonists. However, bimatoprost acid (17-phenyl $PGF_{2\alpha}$), which is found in the aqueous humor of humans after topical application of bimatoprost,(Dahlin et al, ARVO 2004 abstract 2096)[14, 15] exhibits a relatively high affinity for three different PG receptors (i.e., FP [Ki=83nM], EP_1 [Ki=95nM], EP_3 [Ki-387nM]). Bimatoprost acid also exhibits functional activity (phosphoinositide

turnover) at the EP_1 (EC_{50}=2.7nM) and FP (EC_{50}=2.8–3.8nM) receptors in most cell types. [57] Bimatoprost acid is a potent, non-selective $PGF_{2\alpha}$ analog.

Unlike $PGF_{2\alpha}$ or the EP_2 agonist butaprost, bimatoprost did not upregulate orphan nuclear receptor (Nur77) or connective tissue growth factor (CTNF) expression in human ciliary muscle cells or trabecular meshwork. In addition, the FP antagonist, AL-8810 blocked the $PGF_{2\alpha}$-induced Nur77 mRNA expression in human ciliary muscle cells and trabecular meshwork indicating $PGF_{2\alpha}$ -induced Nur77 mRNA expression is via the activation of FP receptors.[36, 37] Bimatoprost induced the upregulation of Cyr61 (cysteine-rich angiogenic protein 61) gene expression in cat iris and human ciliary muscle cells. Cry61 is involved in regulating extracellular matrix-associated signaling proteins and may be a unique mechanism by which bimatoprost exerts its pharmacological action to lower IOP independent of Nur77 or CTNF. [37] The importance of the induction or lack of induction of these various genes for IOP reduction remains to be determined. The production of transgenic mice lacking these genes and their IOP responses to $PGF_{2\alpha}$, bimatoprost, and butaprost is needed.

Bimatoprost appears to reduce the IOP of patients who are unresponsive to latanoprost, [24] suggesting that the prostamide bimatoprost and the FP receptor agonist latanoprost stimulate different receptor populations. This is consistent with studies on isolated iridial cells where bimatoprost stimulated an entirely different cell population to those sensitive to $PGF_{2\alpha}$ and bimatoprost acid (17-phenyl $PGF_{2\alpha}$). [59] An equally plausible explanation is that some eyes may be deficient in corneal esterase and thus are not able to adequately convert the prodrug latanoprost into its free acid active form. [21] Also splice variants of the FP receptor may exist that have not yet been discovered. Single nucleotide polymorphisms in the promoter and intron 1 regions of the FP receptor gene are correlated with the variability in the IOP-lowering response to latanoprost in normal human eyes. [54]

Summary

Clinical and animal studies of aqueous humor dynamics have reported that PG analogs effectively reduce IOP by enhancing aqueous humor outflow. The relative effects of PG analogs on each of the two outflow pathways may vary, but it appears that they reduce IOP predominantly by increasing uveoscleral outflow and to a lesser extent trabecular outflow facility. Morphological studies have identified PG receptors and described significant cellular changes in PG-treated tissues of both outflow pathways. Biochemical studies have reported many complex cellular events in PG-treated outflow tissues, including activation of multiple signaling pathways, and increased expression of some factors and downregulation of others. Genetic studies of knockout mice treated with PGs have found that a reduction in IOP requires intact FP and EP_3 receptors.

Many questions remain unanswered but progress continues to be made. Prostamide antagonists have been described[76, 87] but this has raised new questions. [7] A prostamide receptor needs to be cloned and its biosynthesis enzyme identified to conclude that a unique prostamide-sensitive receptor exists. Further work is required to confirm that bimatoprost acts through this receptor. Multiple-dosing studies of each PG should be compared before concluding that one PG analog acts through mechanisms different from all others. Live animal and clinical studies are needed to support claims made by *in vitro* experiments. Receptor subtype selectivity of topical PGs should be identified. The importance of induction or lack of induction of various genes for IOP reduction needs to be clarified. One day, the current research may lead to future new drugs that exceed the utility of the $PGF_{2\alpha}$analogs.

Method of Literature Search

These studies, dating between 2000 and 2008 were found from a series of literature searches of PubMed and from the reference lists of these articles. The searches included the following terms in various combinations: anterior segment organ culture, aqueous flow, aqueous humor dynamics, bimatoprost, ciliary muscle, DP receptor, EP receptor, fluorophotometry, FP receptor, latanoprost, matrix metalloproteinase, monkey, ocular, outflow facility, prostaglandins, prostamide, prostanoid, tafluprost, tonography, travoprost, unoprostone, uveoscleral outflow. Original research articles, review articles and meeting abstracts are included in this review.

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Table 1

Studies of aqueous humor dynamics in humans and nonhuman primates treated with prostaglandin analogs published from 2000 to 2008

Analog	Subject and n	Duration of treatment	IOP	F_a	C	P_{ev}	F_u	Reference
FP receptor analogs, prostamides								
Bimatoprost	ONT volunteers (n=25)	QD×2 days QD×3 days	↓(day) ↓(night)	↑(day) ↑(night)	↑ day		↑ day	Brubaker et al., 2001 [11]
	OHT or POAG patients (n=29)	QD×7 days	↓	↔	↑		↑	Christiansen et al., 2004 [16]
	ONT volunteers (n=30)	QD×7 days	↓	↔	↑		↑	Lim et al., 2008 [38]
Latanoprost	OHT patients (n=30)	QD×7 days	↓	↔	↔	↔	↑	Toris et al., 2001 [73]
	OHT or POAG patients (n=30)	QD×14 days	↓	↔	↑			Dinslage et al., 2004 [20]
	ONT volunteers (n=30)	QD×7days	↓	↔	↑		↑	Lim et al.,2008 [38]
15-keto latanoprost	Cynomolgus, ONT monkeys (n=30)	One drop	↓	↔	↔			Wang et al., 2007 [77]
Travoprost	OHT & POAG patients (n=26)	QD×17 days	↓(day and night)	↔	↑ (day)	↔	↑ (marginally insignificant)	Toris et al., 2007 [70]
	ONT volunteers (n=30)	QD×7 days	↓	↔	↑		↑	Lim et al., 2008 [38]
	cynomolgus monkeys unilateral OHT (n=12)	BID×3 days	↓	↔	↔		↑[a]	Toris et al., 2005 [71]
Unoprostone	OHT patients (n=30)	BID 5 days and 28 days	↓	↔	↑	↔	↔	Toris et al., 2004 [69]
Tafluprost	cynomolgus monkeys (n=8–12)	QD×4 to 5 days	↓	↑	↔		↑	Takagi et al., 2004 [62]
DP receptor agonist								
AL-6598	cynomolgus monkeys, unilateral OHT (n=11)	BID×3 days	↓ ONT eye only	↑ ONT eye only	↔		↑ ONT eye only	Toris et al., 2006 [72]
EP_2 receptor agonists								
Butaprost	Cynomolgus monkeys, ONT and OHT (n=6–8)	One drop or QD×5 days	↓ OHT and ONT	↔ One drop, ONT	↔One drop, ONT		↑ QD×5 days, ONT	Nilsson et al., 2006 [44]
8-iso PGE_2	Cynomolgus monkeys, ONT(n=7–10)	BID, 9–29 doses	↓	↔	↔ Two methods		↑	Gabelt et al., 2004 [23]

Analog	Subject and n	Duration of treatment	IOP	F_a	C	P_{ev}	F_u	Reference
17-phenyl trinor 8-iso PGE_2	Cynomolgus monkeys, ONT (n=6)	One drop	↓	↔	↑			Wang (ARVO 2007 abstract 4803)
selective EP_4 receptor agonist 3,7-dithia PGE_1	Cynomolgus monkeys, ONT and OHT (n=6–8)	One drop or QD×5 days	↓ OHT and ONT,	↔ One drop, ONT	↑ One drop, ONT		↔ QD×5 days, ONT	Kharlamb (ARVO 2004 abstract 1035)

BID, twice daily; C_{fl}, outflow facility determined by fluorophotometry; F_a, aqueous flow; F_u, uveoscleral outflow IOP, Intraocular pressure; OHT, ocular hypertension, ONT, ocular normotension; P_{ev}, episcleral venous pressure; POAG, primary open angle glaucoma; QD, once daily

↓, decreased effect, ↔, no effect, ↑, increased effect. Blank cell indicates no data reported.

Table 2

Molecular and cellular studies of the effects of prostaglandin-related compounds on the aqueous humor outflow pathways

Analog	Animal/tissue	Duration of treatment	Pathway/effect	Cellular/molecular events	Reference
Trabecular meshwork					
$PGF_{2\alpha}$, fluprostenol	trabecular meshwork strips (bovine)	Up to 2 hours		FP receptor mediated inhibition of endothelin-1 contractility; no effect on baseline tension or carbachol-induced contraction	Thieme 2006 [64]
$PGF_{2\alpha}$	human trabecular meshwork cells	1 hour		FP mediated inositol phosphate accumulation; intracellular calcium release	Anthony 1998[5]
$PGF_{2\alpha}$	human anterior segments	60 minutes per dose	outflow facility unchanged	no change in cAMP production	Dijkstra 1999 [19]
$PGF_{2\alpha}$, butaprost	human trabecular meshwork cells	6 hours		upregulate mRNA for Nur77 and connective tissue growth factor	Liang 2003,2004[36, 37]
Bimatoprost	human anterior segments	48–72 hour continuous infusion	outflow facility increase		Wan 2007 [76]
Bimatoprost	human trabecular meshwork monolayer	48–72 hour continuous infusion	hydraulic conductivity increase		Wan 2007 [76]
Bimatoprost	human trabecular meshwork cells	6 hours		no change in Nur77 mRNA and connective tissue growth factor expression	Liang 2003,2004[36, 37]
bimatoprost acid (B), latanoprost acid (L), travoprost acid (T), unoprostone (U), PGF2α(P)	human trabecular meshwork cells	1 hr (PI turnover); 3 min (Ca^{2+} mobilization)		FP receptor activation: stimulate phosphoinositide turnover (B,L,T,U,P) stimulate intracellular Ca^{2+} mobilization (T,U,P)	Sharif 2003 [58]
latanoprost acid, PGE_1	human trabecular meshwork cells	24 hours		increase mRNA for MMP-1,-3,-17,-24; TIMP-2,-3,-4	Oh 2006 [46]
latanoprost acid; PGE_1	human anterior segments	24 hours	outflow facility increase; scleral hydraulic conductivity unchanged	focal detachment and loss of Schlemm's canal cells; extracellular matrix loss; no change MMPs	Bahler 2008 [6]
latanoprost acid	human trabecular meshwork cells	9 days in vivo		increase insulin growth factor-1 gene and fibroleukin gene expression	Zhao 2003 [91]
Unoprostone	human trabecular meshwork cells	Up to 2 hours		decrease activity of L-type Ca^{2+} channels via tyrosine kinase pathways	Thieme 2005 [65]
PGE_1	human anterior segments	60 minutes	increase outflow facility	increase cAMP production	Dijkstra 1999 [19]
AH13205	human trabecular meshwork cells	Less than 10 minutes		EP_2 agonist activation of BK calcium channels	Stumpff 2005 [61]
Uveoscleral tissues					
$PGF_{2\alpha}$	monkeys	multiple topical treatments		decrease collagen types I, III, IV in ciliary muscle	Sagara 1999 [53]

Analog	Animal/tissue	Duration of treatment	Pathway/effect	Cellular/molecular events	Reference
$PGF_{2\alpha}$	monkeys	multiple topical treatments		increase MMP-1, - 2, - 3 in ciliary muscle	Gaton 2001 [25]
$PGF_{2\alpha}$	monkeys	multiple topical treatments	scleral permeability	increase MMP-1, - 2, - 3 in sclera	Weinreb 2001 [79]
$PGF_{2\alpha}$	human sclera explants			collagen gelatinization	Molik 2006 (ARVO 2006 abstract)
$PGF_{2\alpha}$, latanoprost	human sclera	1–3 days	increase scleral permeability	increase MMP - 1, - 2, - 3	Kim 2001 [33]
$PGF_{2\alpha}$, PhXA85	scleral organ cultures	24 hr		increase mRNA for MMPs and TIMPx	Weinreb 2004 [82]
$PGF_{2\alpha}$, latanoprost acid	human ciliary muscle cells	5 min for ERK1/2, PKC; 4hr for MMP-2 analysis		increase MMP-2 via protein kinase C- and extracellular signal regulated protein kinase 1/2- dependent pathways	Husain 2005 [28]
$PGF_{2\alpha}$, latanoprost acid, bimatoprost acid, travoprost acid	human ciliary muscle cells	1hr for PI turnover; 3 min for Ca2+ mobilization; 5min for p42/p44 MAP kinase		increase mitogen activated protein kinase activity; phosphoinositide hydrolysis; intracellular calcium mobilization; inhibited by FP antagonist AL-8810	Sharif 2003 [56]
$PGF_{2\alpha}$, latanoprost, PhXA85	ciliary muscle tissue (several species)	5–10 min		increase phospholipase A2 and release of arachidonic acid leading to formation of PGE_2, PGD_2 and PGF_{2a}	Yousufzai 1996 [90]
$PGF_{2\alpha}$, butaprost	human ciliary muscle cells	6 hours		upregulate Nur77 and connective tissue growth factor	Liang 2003,2004[36, 37]
latanoprost acid	human ciliary muscle cells	24 hours		increase mRNA for MMP-3, - 9, - 17; increase mRNA for TIMP-3; decrease mRNA for MMP-1, - 2, - 12,-14,-15,-16, TIMP-4	Oh 2006 [47]
latanoprost acid	human ciliary muscle cells	24 hours		increase MMP-1, - 3, - 9	Weinreb 2002 [81]
latanoprost acid	human ciliary muscle cells	Up to 24 hours		increase TIMP-1	Anthony 2002 [4]
latanoprost acid	nonpigmented ciliary epithelial cells	Up to 48 hr		Cyclooxygenase-2 induction leading to increase MMP-1	Hinz 2005 [27]
latanoprost acid	Rats	Single topical dose	Initial IOP elevation followed by prolonged IOP reduction		Husain 2006 [29]
latanoprost acid	human ciliary muscle cells	9 days in vivo		decrease aquaporin-1 and versican gene expression; decrease in mRNA for FP receptor	Zhao 2003 [91]
latanoprost, bimatoprost, sulprostone, AH13205	monkeys	topical treatments for one year		tissue spaces of ciliary muscle enlarged and organized; myelinated nerve fiber bundles present	Richter 2003 [52]
Bimatoprost	human ciliary muscle cells	6 hours		no change in Nur77 and connective tissue growth factor expression; upregulation of Cyr61	Liang 2003,2004[36, 37]

Analog	Animal/tissue	Duration of treatment	Pathway/effect	Cellular/molecular events	Reference
3,7-dithia PGE_1	ciliary muscle tissue (human and monkey)	No details – probably less than 2 hours		no EP_4 mediated relaxation	Kharlamb, 2006 (ARVO 2006 abstract)
Genetic studies					
latanoprost, travoprost, bimatoprost, unoprostone	FP knockout mice	single topical treatment	IOP decrease	FP receptor needed for IOP decrease	Ota 2005 [48]
Latanoprost	FP knockout mice	7 days topical	sclera	intact FP receptor gene needed for upregulation of MMP-2, -3, -9	Crowston 2007 (ARVO 2007 abstract)
latanoprost, travoprost, bimatoprost, unoprostone	EP_1, EP_2, EP_3 knockout mice	single topical treatment	IOP decrease	EP_1 and EP_2 not involved in IOP decrease; EP_3 may have a role	Ota 2005 [48]

IOP, intraocular pressure; MMP, matrix metalloproteinase; PG, prostaglandin; PI, phospholipase C-mediated phosphoinositide; TIMP, tissue inhibitor of metalloproteinase;