Neuroaxonal and cellular damage/protection by prostaglandin receptor ligands, fatty acid derivatives and associated enzyme inhibitors

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Abstract
Cellular and mitochondrial membrane phospholipids provide the substrate for synthesis and release of prostaglandins in response to certain chemical, mechanical, noxious and other stimuli. Prostaglandin D₂, prostaglandin E₂, prostaglandin F₂α, prostaglandin I₂, and thromboxane-A₂ interact with five major receptors (and their sub-types) to elicit specific downstream cellular and tissue actions. In general, prostaglandins have been associated with pain, inflammation, and edema when they are present at high local concentrations and involved on a chronic basis. However, in acute settings, certain endogenous and exogenous prostaglandins have beneficial effects ranging from mediating muscle contraction/relaxation, providing cellular protection, regulating sleep, and enhancing blood flow, to lowering intraocular pressure to prevent the development of glaucoma, a blinding disease. Several classes of prostaglandins are implicated (or are considered beneficial) in certain central nervous system dysfunctions (e.g., Alzheimer’s, Parkinson’s, and Huntington’s diseases; amyotrophic lateral sclerosis and multiple sclerosis; stroke, traumatic brain injuries and pain) and in ocular disorders (e.g., ocular hypertension and glaucoma; allergy and inflammation; edematous retinal disorders). This review endeavors to address the physiological/pathological roles of prostaglandins in the central nervous system and ocular function in health and disease, and provides insights towards the therapeutic utility of some prostaglandin agonists and antagonists, polyunsaturated fatty acids, and cyclooxygenase inhibitors.

Key Words: AL-8810; axon; brain; central nervous system; cyclooxygenase inhibitors; neuron; neuroprotection; ocular; polyunsaturated fatty acids; prostaglandins

Introduction
Prostaglandins
Arachidonic acid formed by the action of phospholipase A₂ on cell membrane phospholipids is the major substrate for future conversion by lipoxigenases to create leukotrienes, and for cyclooxygenases (COX-1[constitutive] and COX-2 [inducible by inflammatory stimuli]) to form prostaglandins (PGs) via PGG₂ and PGH₂ (Coleman et al., 1994). The five distinct active biofluidic lipid molecules created by COX-1 and COX-2 include PGG₂, PGE₂, PGF₂α, PGI₂, and thromboxane-A₂ (TXA₂) (Coleman et al., 1994; Figure 1). The biological actions of the major prostaglandins are mediated by separate receptors whose names originate from these PGs and are known as DP, EP, FP, IP, and TP receptors, respectively (Coleman et al., 1994). Some of these major receptors have sub-types such as DP₃, DP₄, EP₁, EP₂, EP₃, EP₄, TP₁, and TP₂ receptors (Figure 1). Some additional derivatives of PGD₂, including PGJ₂ and deoxy-PGJ₂ for instance, have various biological functions either through activating DP receptors or via cross-talk with other receptors/pathways such as transient receptor potential cation channels to cause inflammation and pain (Jang et al., 2020). Some specific inhibitors of COX-1 and COX-2 have been developed later as therapeutics to treat pain and other conditions and these will be discussed later (Patrignani and Patrono, 2015).

Prostaglandin receptors, signal transduction and general actions
The heptahelical guanine-nucleotide-coupled-receptors associated with these PGs are embedded in the plasma membranes of the majority of the mammalian cells, and transduce either an elevation (DP-, EP₂-, EP₄-, and IP-receptors) or reduction (EP₃-receptors) of cAMP (Narumiya et al., 1999; Woodward et al., 2011). Activation of the remaining PG receptors (EP₁, FP- and TXA₂-receptors) by their respective agonist ligands results in the production of intracellular inositol phosphates (IPs) that in turn raise intracellular Ca²⁺ ([Ca²⁺]) by releasing it from the endoplasmic reticulum of the cells (Narumiya et al., 1999; Woodward et al., 2011), and diacyl glycerol that activates various enzymes (Figure 1). These changes in [Ca²⁺], diacyl glycerol, and cAMP then evoke downstream signal transduction such as phosphorylation and activation of various kinases, culminating in the final biological activity of the eicosanoid (e.g., enzyme or hormone release, muscle contraction or relaxation, platelet aggregation, pain induction, and lowering of intraocular pressure) (Coleman et al., 1994; Smyth et al., 2000). Some receptor-selective agonists and antagonists have also been developed and introduced into medical treatments of some diseases that will be discussed below.

Preformed or newly synthesized PGs mediate numerous biological functions such as causing cytokine release, enhancing fluid hydrodynamics, contracting or relaxing smooth muscles, initiating hormone and growth factor secretion, eliciting pain, causing fever, modulating gene expression as destructive agents, or enhancing cellular survival. Some of these actions are paradoxical and reflect the pro- or anti-inflammatory properties. PGs can exhibit different actions depending on their acute or chronic release, their concentrations, cell types involved, and site(s) of action. Regarding inflammation, for instance, PGs in the acute phase are usually protective, while in chronic situations, they become destructive, especially when their concentration remains elevated for a protracted time frame. This “Jekyll and Hyde” nature of PGs is reflected by activities of cytokines where certain forms are pro-inflammatory (e.g., interleukin-1 (IL-1), IL-6 and IL-8), whereas others are generally anti-inflammatory (e.g., IL-10, IL-17, and IL-37) (Akdis et al., 2016). Interestingly, in many circumstances, PGs regulate the synthesis and secretion of certain cytokines and thus there is a complex relationship between these cellular mediators due to feed-forward and feedback mechanisms that involve the immune system.

As often happens in nature, body tissues and cells self-regulate to maintain homeostasis. This ying-yang nature of mediators of communication and inflammation is evident in the eicosanoid field. Thus, whilst endogenous PGs are generally nonspecific in their receptor selectivity (Table 1), as compared to synthetic PGs (e.g., FP-receptor agonists; Table 2), and cause inflammation, docosahexaenoic acid (DHA), an omega-3 fatty acid that is a primary structural component of the human brain, skin, and retina, is anti-inflammatory. DHA comprises 40% of the polyunsaturated fatty acids (PUFAs)

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How to cite this article: Sharif NA (2023) Neuroaxonal and cellular damage/protection by prostaglandin receptor ligands, fatty acid derivatives and associated enzyme inhibitors. Neural Regen Res 18(1):5-17.
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In the brain and 60% of the PUFAs in the retina and is derived mainly from food sources and some are endogenously synthesized from α-linolenic acid (Figure 2). The neuronal plasma membrane contains up to 50% DHA, which modulates the carrier-mediated transport of choline, glycine, and taurine, the function of delayed rectifier potassium channels, and the response of rhodopsin contained in the synaptic vesicles. Phosphatidylinerine, which has a high DHA content, has roles in neuronal signaling and neurotransmitter synthesis, and DHA deficiency is associated with cognitive decline (Cedarholm et al., 2013). DHA levels are reduced in the brain of severely depressed people (McNamara et al., 2013). The conversion of DHA to the anti-inflammatory lipids, neuroprotection D1, and D- and E-resolvins (Figure 2), is the basis of DHA’s beneficial properties in neuronal functions and in preventing or reducing oxidative stress in many diseases (Kim and Spector, 2018).

Prostanoids in Neurological Functions: Do They Help or Hinder?

Lipids perform many structural and functional roles within the central nervous system (CNS), both within the grey matter (neuronal elements) and the white matter (axonal elements). Therefore, it is to be expected that any malfunction associated with neuronal or axonal lipid metabolism or structural defects involving membranes of the cell exterior and/or intracellular organelles would have major deleterious consequences. Accordingly, in pathological situations, the cellular machinery would mobilize its resources to combat the disease processes by modulating lipid metabolism and altering gene expression to augment reparative and survival counter-measures. Below are presented a range of roles of PGs and their downstream signaling pathways involved in CNS and ophthalmic diseases and the potential utility of synthetic PG receptor agonists and antagonists to ameliorate these conditions. Due to the multiplicity of PGs and their receptors, the interplay between them sometimes yields conflicting conclusions indicating the complexity of their effects (Yagami et al., 2016). To better understand the roles that various PG receptors may play in CNS, their relative presence and distribution need to be understood. Accordingly, using thin-layer chromatography, Holmes and Horton (1968) showed the presence of endogenous PGD\(_2\), PGE\(_2\), and PGF\(_\text{II}\) in dog brain cortex, hippocampus, caudate nucleus, hypothalamus, cerebellum, medulla, and pons, cortical white matter, and spinal cord. Additionally, in situ hybridization (Suzuki-Yamaoto et al., 1994; Zhang et al., 1995; Candelario-Jalil et al., 2005), autoradiography (Yamashita et al., 1983; Matsumura et al., 1992, 1995; Olda et al., 1997) and immunohistochemistry (Nakamura et al., 2000) revealed presence of the genes and their products on PG receptors in numerous mammalian CNS tissues (Table 3).

Database Search Strategy

This narrative review article was constructed using the information gathered, assembled, and harmonized from publications revealed using PubMed of the National Institute of Health (NIH), National Library of Medicine (PubMed.org), and Google. Searches were performed till June 2021. The search strategy and selection criteria utilized keywords and combinations thereof such as prostanoids and brain; prostanoids and eye or ocular; prostanoids and disease; prostanoids and protection; prostaglandins and neuroprotection; prostaglandins and neurodegeneration; inflammation and prostanoids. No limit was placed on the year of publication or authorship. During the assembly of various references for each section of the review article, particular attention was paid to using relatively recent review articles on given topics where possible, with emphasis on the last decade. Sometimes, it was necessary to cite original ground-breaking research discovery publications to give the credit to the original authors and thus older citations were used. However, pertinent materials and information reported over the last 30 years were accounted for in formulating opinions and being as factual as possible.

**Figure 1** The generation of various prostanoids and their receptor activation and signaling profiles.

The figure illustrates how PLA\(_2\) hydrolyzes membrane-bound phospholipids to generate arachidonic acid which then acts as a source for the synthesis of endogenous prostaglandins by COX-1 and COX-2 through the intermediary PGH\(_2\). The major prostanoid receptors and their signal transduction pathways/mechanisms triggered by the PGs are also depicted. The figure was adapted and modified from Ganesh (2014). COX: Cyclooxygenase; PG: prostaglandin; PLA\(_2\): phospholipase A2.

**Figure 2** The PUFA-derived cytoprotective/neuroprotective agents and their biological actions.

PUFA-derived protectins, neuroprotectins, and D-series resolvins coupled with their cellular and molecular actions leading to final anti-inflammatory and protective actions are shown on the right side of the figure. The left side of the figure shows the generation of lipoxins from arachidonic acid and E-series resolvins from eicosapentaenoic acid and their specific actions which differ from those of protectins and D-series resolvins. The figure was adapted and modified from Serhan (2010). CCR: Chemokine receptor; COX: cyclooxygenase; DC: dendritic cell; IL: interleukin; I/R: ischemia reperfusion; LX: lipoxin; NP: neuroprotectin; NFκB: nuclear factor kappa B; PD: protectin; PG: prostaglandin; PMN: polymorphic neutrophil; ROS: reactive oxygen species; RV: resolvin; TLR: Toll-like receptor; TNF: tumor necrosis factor.

**Table 3** Relative presence and distribution of genes and their products on PG receptors in numerous mammalian CNS tissues.
Alzheimer’s Disease

Alzheimer’s disease (AD) and the associated dementia/memory loss is one of the most frightening neurological diseases afflicting humans on a global scale (at least 44 million patients worldwide, with ~6 million in the US). Despite decades of research, the exact etiology of AD has remained elusive, and thus even a minor improvement in signs and symptoms of this disease would be most welcome by the patients and their caregivers. Unfortunately, a milieu of endogenous agents and inter-connected pathways conspire to induce AD, and thus a singular curative therapeutic agent or device is unlikely to be successful in combating AD. However, in addition to the accumulation of amyloids and Tau and related misfolded proteins causing brain cellular damage in AD, multifactorial chronic inflammation appears to be one major root cause of AD, and it is now believed that PGs may play a role in the death of neurons. The schematic shows the ways cell death can be induced by stress (e.g., oxidative), cytokines, and PGs in stroke. Adapted and modified from Jayara et al. (2019). AIF: Apoptosis inducing factor; AMD: age-related macular degeneration; Apaf: apoptotic protein activating factor; BBB: blood-brain barrier; CASP: caspase; Cyt: cytochrome; DAMPS: danger associated molecular patterns; PUFA: poly unsaturated fatty acid.

Table 1 | Relative affinities and receptor selectivities of natural prostaglandins for PG receptors and some receptor subtypes

| Natural PG | DP | EP<sub>1</sub> | EP<sub>2</sub> | EP<sub>3</sub> | FP | IP | TP |
|-----------|----|-------------|-------------|-------------|----|----|----|
| PGE<sub>1</sub> | >10000 | 26±10 | 4.9±0.5 | 3±0.2 | 0.9±0.03 | 3400±710 | 5370±8 2136 | 3±3581 vs. EP<sub>1</sub> | >10000 | >667 vs. EP<sub>1</sub> |
| PGF<sub>2α</sub> | 18000±6400 | (×138) | 594±12 | 24±8 | 43±3 ± 23 | 13066±5000 | ×385 | ≥19000 | (×1462) |

Table 2 | Relative affinities of synthetic FP-receptor agonist against prostaglandins for various PG receptors and some receptor subtypes, and their relative selectivities against non-FP-receptors

| PG Analog | DP | EP<sub>1</sub> | EP<sub>2</sub> | EP<sub>3</sub> | FP | IP | TP |
|-----------|----|-------------|-------------|-------------|----|----|----|
| Travoprost (Free acid) (IS)-Flurpropastrol | 52000±7200 | (×1486) | 95±00±1240 | (×273) | >12900±1240 | 594±12 | 24±8 | ≥50000 | (×126) |
| Bilatroprost (17-phenyl-PGF2α) (Free acid) | >90000±1084 | (×510) | 95±00±1240 | (×273) | >12900±1240 | 594±12 | 24±8 | ≥50000 | (×126) |
| Latanoprost (PHXAS) | →20000±(×204) | 2060±688 | (×21) | 39±667±5558 | (×428) | 7519±879 | (×77) | 7500±2830 | (×765) |
| Unoprostone (Free acid) | >30000±(×77) | 11700±2710 | (×21) | 39±667±5558 | (×428) | 7519±879 | (×77) | 7500±2830 | (×765) |

Table 3 | Central nervous system localization and distribution of prostanoid receptors determined by various techniques

| PG receptor/ sub-types | Primary intracellular second messenger | CNS tissues/cells expressing PG receptors |
|------------------------|--------------------------------------|----------------------------------------|
| DP<sub>1</sub> | Elevation of cAMP | Choroid, leptomeninges, thalamus, medulla oblongata (brainstem), cortex, and hippocampus |
| DP<sub>2</sub> | Elevation of cAMP | Hippocampus, thalamus, cortex, and brainstem |
| EP<sub>1</sub> | Elevation of IPs and [Ca<sup>2+</sup>] | Thalamic area, hypothalamus, cerebral cortex, hippocampus, striatum, and cerebellum |
| EP<sub>2</sub> | Elevation of cAMP | Cerebral cortex, striatum, hippocampus, thalamus, and spinal cord |
| EP<sub>3</sub> | Reduction of cAMP | Thalamic area, hypothalamus, cortex, hippocampus, and striatum |
| EP<sub>4</sub> | Elevation of cAMP | Hypothalamus, thalamus, hippocampus, striatum, and cortex |
| FP | Elevation of IPs and [Ca<sup>2+</sup>] | Hippocampus, cerebral cortex |
| IP | Elevation of cAMP | Cortex, hippocampus, striatum, spinal cord (dorsal horn), trigeminal nucleus, and nucleus of the solitary tract |
| TP | Elevation of IPs and [Ca<sup>2+</sup>] | Hippocampus, cerebral cortex, and white matter |

cAMP: Cyclic adenosine monophosphate; CNS: central nervous system; IPs: inositol phosphates; PG: prostaglandin.
Additional evidence of PGs involvement in AD etiology concerns enhanced cerebral COX-1/2 expression (Yasojima et al., 1999; Hoozemans et al., 2001), detection of abnormally high levels of PGE₂ in the cerebrospinal fluid of AD patients (Montine et al., 1999), and EP₃ receptor-induced elevation of amyloid-β precursor mRNA and protein (Pooler et al., 2004; Hoshino et al., 2010; Herbst-Robinson et al., 2015). An interesting observation relates to an apparent selective down-regulation of EP₃ receptor by PGE₂, which continues to activate EP receptors with a resultant increase of the β-amyloid concentrations (Hoshino et al., 2009). Linkage of EP receptors activation to AD pathogenesis has now been confirmed in a mouse model of AD where knocking out the EP3 receptor resulted in reduced oxidative cerebral damage and β-amyloid levels (Liang et al., 2005), and no apparent loss of mouse spatial memory (Savonenko et al., 2009). Additionally, microglia that lack EP₃ receptors are less prone to toxic effects of β-amyloid and appear to ingest and degrade these toxins (Shie et al., 2005). Furthermore, EP₃ receptor activation by TNF-α-mediated elevation of PGE₂, in rat astrocytes elevates cellular nitrates and nitrates that can kill neurons (Hsiao et al., 2007). While EP₃ receptors appear to play a central role in AD (Wei et al., 2010; Prio et al., 2012), despite a recent report that illustrates protective effects of an EP₁/EP₃ receptor agonist (misoprostol; Tian et al., 2016), elevated PGE₂ concentration and activated DP, EP₃ receptor expression on astrocytes and astrocytes within senile plaques of AD patient brains, and in animal models of the disease, suggest the involvement of DP receptors in AD as well (Mohri et al., 2007). Consistent with these reports is the intriguing possibility that other PGs derived from PGD₂ for example by dehydrogenation leading to the formation of detrimental J2-PGs (derived from PGD₂), also play a role in causing or amplifying the disease process by dampening the ubiquitin-proteasome/mitochondrial pathway (Figueiredo-Pereira et al., 2015).

Based on the intense search for potential beneficial remedies towards AD, numerous therapeutic approaches have been proposed and some are in late stages, involving the inhibition of COX-2 (Kumari et al., 2020). Whilst recognizing the role that PGs (in particular PGE₂ and PGD₂) play in the inflammatory cascade-connected to AD pathogenesis (see above), only first-generation COX-inhibitors (indomethacin; ibuprofen), and recently, novel COX-5/LOX inhibitors (e.g., Licoferone; Kumar et al., 2020; Razavi et al., 2021), seem to have been tested in the AD patients, and no other PG-receptor-related targets appear under investigation (Cummings et al., 2017). The latter enzyme inhibitors appear not to show any significant benefits in AD-patients. However, there is some new hope on the horizon. With the recent advent and characterization of small molecule antagonists of COX-1 and COX-2 inhibitors protected substantia nigra neurons (Mattammal et al., 1995) was observed. Many preclinical studies would need to be performed first to select the optimum compound(s) for testing in the clinic. DP, receptor antagonists (e.g., BW-A868C, S-5751, ONO-AE3-237, and Laropiprant; Figure 5) and EP₃ receptor antagonists (e.g., PF-04418948, TG4-155, TG6-10-1, TG6-129, and AH-6809; Ganesh, 2014, Figure 6) are recommended to be screened for their efficacy against oxidative stress, amyloid-β-induced toxicity, etc using cortical/hippocampal neurons and astrocytes obtained from mice with experimentally-induced AD. Efficacious DP and EP₃ receptor antagonists could then be tested alone or in combination. Additional combination therapy could exploit suitable COX-1 and COX-2 inhibitors since they improved spatial learning and memory in triple transgenic mice by lowering amyloid accumulation and tau phosphorylation (Cakala et al., 2007; Choi et al., 2013). Should the afore-mentioned non-clinical strategy be successful, the stage would be set for evaluating and translating these findings in the clinical setting with AD patients. However, as COX-2 is induced after local inflammation, it may be better to stratify the patient population so that AD pathology and thus treatment could be staged to account for different development and severity of the disease.
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Dopaminergic neurons in culture (Carrasco et al., 2008), whether such efficacy can be realized in PD patients remains to be determined. The recent availability of a novel COX-5/LOX inhibitor, lclofenol (Kumar et al., 2020; Razavi et al., 2021) may help in this regard.

A recent study involving 6-hydroxydopamine induced neurotoxicity in a neuroblastoma cell line (SH-SY5Y) via oxidative stress demonstrated protective effects of FP-receptor agonists, fluprostanol, and PGE₂₃ (Figure 8; Sano et al., 2021). These compounds decreased the intracellular reactive O₂⁻ species levels and promoted activation of the endogenous anti-oxidant gene expression systems, activities that were blocked by the FP-receptor antagonist, AL-8810 (Figure 8).

Stroke, Traumatic Brain Injury, and Epilepsy

Serious debilitating disorders of the brain such as stroke (the single largest cause of adult disability in the developed world accounting for 600,000/year cases in the US), epilepsy, and traumatic injury (e.g. injury caused by impact) are usually caused by vascular abnormalities or damage to cerebral blood vessels and thus the accompanying ischemia/hypoxia. The resulting reduction in blood flow deprives the neurons of precious energy and oxygen and causes profound oxidative stress (middle cerebral artery occlusion of rodents has been used as a reliable and predictive model of stroke. Using such a mouse model of stroke, prior intravenous treatment with FP-receptor (FP-R) antagonist (AL-8810) markedly increased the cortical infarct volume and provided a faster commensurate motor recovery in the mice (Kim et al., 2012). Such structural and functional outcomes were confirmed in other mice whose FP-Rs had been genetically deleted (Kim et al., 2012), thereby confirming the involvement of endogenous PGs, in the coupling the stroke symptomatology and the ischemic events. In addition, oxygen-glucose-deprived mouse hippocampal slices and cultured hippocampal neurons, the FP-R-antagonist also afforded protection by curbing the generation of highly reactive species and thus concomitant brain damage (Kim et al., 2012). These studies, therefore, provided strong evidence that AL-8810 and other FP-R-antagonists, such as BAY-6672 (Beck et al., 2020) may be useful therapeutic agents in the treatment of stroke and other ischemic diseases (Figure 6).

The potential use of EP-receptor antagonists may also be beneficial in the management of stroke since SC51089 and SC51322 prevented the damage to rat hippocampal slices under O₂⁻/glucose-deprivation conditions (Zhou et al., 2008). However, a report by McCulloch et al. (2002) using isolated hippocampal neurons placed under NMDA-induced excitotoxic and hypoxic conditions indicated that activation of EP2 receptors may be neuroprotective in cerebral ischemic challenges. Likewise, 15-deoxy-(16-m-tolyl)17,18,19, 20-tetranorso-carbacyclin methyl ester, a selective CNS-type IP receptor agonist, abrogated brain damage in an animal model of stroke (Takamatsu et al., 2002). Since a milieu of prostanoids appears to be implicated in the pathophysiology of stroke, however, a cocktail of COX- and lipooxygenase inhibitors may be beneficial in tackling signs and symptoms of stroke associated with chronic cerebrovascular diseases (Singh et al., 2020). More research is needed using modern techniques and novel PG agonists and antagonists to tease out the exact involvement of PG receptors in causing or preventing damage in the hippocampus and cerebral cortical tissues during and after stroke or stroke-like trauma of the brain.

In an allied field to stroke, traumatic brain injury (TBI) is common and is often linked to brain damage and death in the elderly. An initial contusion followed by hematoma, subarachnoid hemorrhage, and diffuse injury, and death of the axons of brain neurons is hallmark features of TBI. Neuronal inflammation combined with oxidative stress and ischemia/hypoxia that follows the contusion represents the second phase of TBI and the accompanying loss of various bodily functions including speech and neuromuscular activity. Several researchers have reported elevated generation and release of pro-inflammatory PGs, including PGF₂α, during and after TBI as a result of increased oxidative stress and impaired availability of arachidonic acid and enhanced COX-2 activity (Glushakov et al., 2013a, b). Interestingly, increased COX-2 levels have been observed in the ischemic cerebral and adult human brain, and in an experimental mouse model of TBI, Glushakov et al. (2013a, b) noted the beneficial role of COX-2 inhibitors after intracerebral injection of an FP-R antagonist (AL-8810) decreased hippocampal swelling and improved the neurological deficit scores 1- and 2-days post-TBI insult. Therefore, it appears that PGs and PG receptor agonists could be used to prevent brain damage and help preserve the functional integrity of the cerebral cortex and hippocampus after and during the TBI events. Recently, an EP₂ receptor agonist (AH6809) lowered the production of inflammatory mediators in the hippocampus after cerebral concussion in rats (Li et al., 2018), indicating that endogenously released PGE₂ may have protective effects in TBI, a finding supported by in vitro studies in hippocampal slices (You et al., 2018). The potential utility of other PG agonists to chronic brain injury (e.g., caused by aluminum or iron) is exemplified by the neuroprotective effects of an IP-receptor agonist, beraprost (Pan et al., 2015).

Disturbance of brain electrophysiology via loss of ionic homeostasis leads to phenomena known as cortical spreading depolarization (or depression) (CSD) (Kramer et al., 2016; Cozzolino et al., 2018). CSD often leads to vascular dysfunctions such as vasospasm and vasoconstriction resulting in reduced cerebral blood flow and volume and is implicated in neurological disorders including migraine, epilepsy, intracranial hemorrhage, and TBI. These conditions result in significant disability and morbidity around

Multiple Sclerosis

The global prevalence of multiple sclerosis (MS) is estimated to be around 2.5 million people of which nearly 400,000 cases exist in the US. MS is an autoimmune disease characterized by the loss of myelin around the axons of neurons that form the nervous system (Pachner et al., 2011). Since nerves control every organ, MS adversely impacts all bodily functions. Unfortunately, however, it has been very difficult to study MS in vitro and in vivo to delineate the precise etiology of MS. Some progress has been made using a rodent model of MS involving experimental autoimmune encephalomyelitis in which PGs are major or critical (Kalyvas and Davids, 2004; Kalyvas et al., 2009; Ayoub et al., 2011). The latter is supported by observations of concomitant elevation of COX-1, COX-2, and PLA2 activity, and levels of PGE₂ and PGF₂α in the spinal cord and cerebellum of experimental autoimmune encephalomyelitis-afflicted rodents (Bolton et al., 1984; Pollak et al., 2003; Ayoub et al., 2011). Furthermore, inhibitors of COX-1/2 and PLA2 reduced the symptoms and behavioral effects associated with experimental autoimmune encephalomyelitis (Reed et al., 1994; Marusić et al., 2008). More promising therapeutic intervention pertains to the use of an FP-receptor antagonist (AL-8810; Griffin et al., 1999; Sharif et al., 2000; Sharif and Klitzko, 2019; Figure 8) in reducing myelin loss and movement disorder in a mouse model of MS by using copper-based toxin (Williams et al., 2014). Such data offer some hope for future symptoms-relief in MS-related motor dysfunctions. Since a more potent FP-receptor antagonist than AL-8810 has recently been discovered, BAY-6672 (Figure 6; Beck et al., 2020) may be worth evaluating in animal models of MS and perhaps tested for clinical efficacy and utility.

Amyotrophic Lateral Sclerosis

Death of neurons and their axons located in the spinal cord, brainstem motor nuclei, and motor cortex are hallmark characteristics of amyotrophic lateral sclerosis (ALS). This disease afflicts > 20,000 people in the US at any one time, with as many as 6000 newly diagnosed patients each year. While the sporadic form accounts for >90% of the total ALS cases with unknown etiology, the inherited form is associated with mutations of the superoxide dismutase-1 (Julin, 2001). Elevated levels of COX-2 (Almer et al., 2001) and PLA₂ activity (Shibata et al., 2010) were reported in postmortem spinal samples ALS patients, in both sporadic and familial forms of ALS. Consequently, increased levels of PGE₂ were observed in the CSF of ALS patients (Almer et al., 2002), and EP₂ receptors participate in accelerating the progression of the disease in an animal model of ALS (Liang et al., 2008). Therefore, antagonism of the EP₂ receptor may prove beneficial in slowing the progression of ALS. However, an earlier report had described the beneficial effects of PGE₂ (Blak et al., 2004), but the receptor subtype(s) involved was not delineated. With the relatively recent advent and availability of selective EP-receptor antagonists (Woodward et al., 2011; Ganesh, 2014; Figure 6), the detrimental or beneficial role(s) of PGs in combatting ALS could be ascertained shortly, at least in animal models of ALS.

Figure 7 | Chemical structures of EP₂, EP₃, EP₄, and EP₅ receptor antagonists.

Figure 8 | Chemical structures of FP-receptor agonists and antagonists.
the world. The involvement of endogenous PGs during CSD/oligemia development was demonstrated in rats by Gariepy et al. (2017). The initial phase of oligemia/CSF involved activation of COX-1 and production of TXA2, while the second phase was mediated by PGF2α, derived from metabolism of COX-2 activity. Consistent with this was the finding that AL-8810 prevented only the second phase of oligemia and consequently increased cerebral blood flow/volume (Gariepy et al., 2017). Taken together, such studies provide support for the potential clinical utility of TXA2-R and FP-R antagonists (Gariepy et al., 2017; Sharif and Klimko, 2019; Beck et al., 2020) and also EP receptor antagonists (e.g., L-161982; Varga et al., 2016) to treat CSD and overcome the pathologically reduced brain blood flow/volume.

Epileptic seizures have numerous instigators, and several medicinal products are available to treat this disorder (Chung et al., 2011). However, there’s also an hunger for new drugs to treat recipients or those whose current therapies are insufficient or are contraindicated. Relative to the potential roles of endogenous and exogenous PGs in either starting or curtailing seizure activity, kainic acid-induced seizure models using rodents haven’t failed to reveal the effective role of PGs in controlling seizure activity. Studies, Kim et al. (2012), showed that either COX-2 inhibitor or, FP-R antagonist AL-8810 injected intracranially before kainic acid-induced seizures potentiated the seizure activity. As a corollary, ic-injection of PGF2α but not PGE2, significantly reduced kainic acid-induced seizures (Kim et al., 2008), thereby suggesting the involvement of FP-Rs in the beneficial effects of endogenously released PGF2α in maintaining cerebral/hippocampal electrical activity homeostasis. However, additional studies are needed to corroborate these observations and to elaborate on the complex roles of PGs and inflammatory mediators in modulating seizure activity (Shimada et al., 2014; Santos et al., 2017). Also, since numerous FP receptor-selective agonists are now available (e.g., latanoprost, travoprost, and tafluprost) the role of FP-receptors in controlling seizure activity is worthy of pursuit. With continuing research, the role of EP2 receptors mediating epileptic conditions has been recently verified where high-affinity brain-permeable EP2-receptor-selective antagonists (TG4-155, TG6-10-1, TG8-260) ameliorated seizure-induced damage in various rodent models of status epilepticus (Nagib et al., 2020; Rojas et al., 2021). Likewise, since a new generation of COX5-LOX inhibitors like liceofene (Payandemehr et al., 2015; Razavi et al., 2021) exhibited anti-convulsant characteristics in mice, this class of enzyme inhibitors for future treatment of epilepsy may be warranted, especially as adjunctive therapies.

Prostaglandins in Mediating Pain

PGs have been associated with mediating inflammation and pain for several decades leading to the discovery of aspirin as a universally acceptable COX-1 inhibitor (Vane, 1971). However, due to different types of peripheral and deep pain categories and various noxious stimuli that can trigger pain, COX inhibitors alone are not particularly effective analgesics due to their relatively short duration of action and stomach-irritation causing effects although their antiinflammatory and pain-reducing properties are still much appreciated. To delineate the various roles of DP-, EP-, FP-, IP- and TXA2 receptors in stimulating nociceptor responses due to heat, mechanical and formalin-induced pain, mice lacking these receptors due to genetic deletions were utilized (Popp et al., 2009) demonstrated that COX-1 and EP3-receptor knockout mice exhibited reduced heat-evoked pain, while COX-2 and EP1 receptor knockout mice had reduced licking response to formalin injections. Interestingly, heat-induced pain sensitivity was enhanced in FP-, EP-, and EP1-dependent mice, whilst DP2 and EP4 knockout mice displayed greater responses in the formalin test (Popp et al., 2009). IP- and TXA2-deficient mice exhibited normal behavior in all the afore-mentioned pain-inducing challenges. These data strongly suggested that pain processing signaling due to various stimuli is differentially propagated and handled at the level of the spinal cord and the brain, thereby reinforcing the notion that a single PG receptor subtype-directed drug is unlikely to provide a high magnitude and long duration of analgesic efficacy. Even though the usefulness of such gene-knockout strategies is limited by potential compensation by the remaining PG receptors in these animals, other studies have shown that PGE2, via EP3-receptors and prostacyclin via IP-receptors sensitize TRPV1 capsaicin-channels (Moriyama et al., 2005), DP, (Wright et al., 1999) and EP-receptors mediate spinal inflammatory hyperalgesia (Reinhold et al., 2005), and EP1-receptors and kappa-opioid receptors cooperate in transducing tactile pain (Mimami et al., 2003). Moreover, Kunori et al. (2009) reported that mechanical allodynia induced by intrathecal administration of PGF2α, and ATP was propagated via capsaicin-activated primary afferent pathway within the spinal cord, and supportive evidence was gathered using FP-R knock-out mice in which neither δ-methylene ATP nor PGF2α elicited allodynia. However, since an FP-R antagonist, AL-8810, curtailed the allodynic pain induced by intrathecal δ-methylene ATP in wild-type mice, it was concluded that activation of the P2X3 receptors to cause the pain-response was ultimately being mediated via FP-Rs that are co-located with P2X3 receptors in the spinal cord (Kunori et al., 2009). Gatta et al. (2012) then reported that direct spinal administration of PGF2α into healthy mice potently excited nociceptive neurons and this activity was also abolished by AL-8810. Collectively, there is the active participation of various PG-receptors in mediating different forms of afferent signals and thus future combination medicinal products can be envisaged being formulated in different permutations encompassing COX-1/2 inhibitors + FP-receptor antagonists (AL-8810; BAY-6672; Figure 8), or COX-1/2 inhibitors (Figure 4) + EP1- and EP2-receptors (Figure 6) and FP-receptor antagonists (Figure 8), depending on the need of the patient. Such formulations would provide alternative therapies for combating pain without resorting to the use of opioid drugs and dealing with all the undesirable side-effects of the narcotics.

Schizophrenia and Refractory Depression

Only a few studies have been conducted to determine the potential role(s) of PGs in schizophrenia and refractory depression and have been summarized (Yui et al., 2015). Since elevated levels of PGE2, and/or other PGs were reported in subsets of patients with both these psychiatric disorders, COX-2 inhibitors were tested for potential benefits. Unfortunately, mixed results were observed thereby warranting further investigations of the causal relationship between prostanoids and such diseases.

Pathological/Beneficial Role of Prostaglandins in Ocular Functions and Disorders

Based on early research in the ocular field, endogenous and exogenous PGs demonstrated inflammatory effects causing edema and pain, and thus earned a bad reputation (Vane 1971; Bhattacherjee and Coles, 1977). However, in the late 1980s-early 2000s, it was discovered that certain esterified PGs have beneficial effects in the eye in certain cases when dosed topical ocularly (t.o.). One particularly useful effect of FP-receptor agonist dorzolamide, is its ability to cause the aqueous humor (AH) to drain from the anterior chamber (AC) of the eye to reduce elevated intraocular pressure (IOP), this being a major risk factor for the development of glaucoma, the second leading cause of blindness (Stjernschantz and Bito, 1989; Sharif et al., 1999; Figures 10 and 11) and using functional assays (Figures 12 and 13) suggested a variety of physiological and/or pathophysiological actions of PGs in the eye. Some aspects of such will now be discussed below.
Autoradiographic localization of PG receptors in human ocular tissues using various radioligands. The ability of travoprost free acid to activate functional FP-receptors on isolated human conjunctival epithelial cells.

Total and non-specific binding of [3H]-PGF2α to FP-receptor in consecutive 10 μm thin sections of whole postmortem human eye. (C) Distribution of [3H]-PGE1, radiolabeled EP-receptor binding (total) and non-specific (D), respectively. (E, F) [3H]-BW828C-radiolabeled DP-receptor binding (total and non-specific, respectively) to anterior segment sections of postmortem human eyes. The figures were adapted and modified from Sharif et al. (1999, 2002b, 2004). The image analysis system permitted pseudo-color-coding of the acquired autoradiograms that follow the prismatic color-coding to depict the relative density of the receptor binding sites, with red being the highest and blue being the lowest. Actual quantitative data obtained for the different PG receptors located in various ocular tissues after digital subtraction of the non-specific binding images are available in the articles by Sharif et al., (1999, 2002, 2004). CCM: Circular ciliary muscle; CHO: choroid; COR: cornea; CP: ciliary process; ISM: iris smooth muscle; LCM: longitudinal ciliary muscle; RET: retina.

Figure 10 | Autoradiographic localization and visualization of various PG receptors in human ocular tissues using various radioligands.

Figure 11 | Autoradiographic localization of PG receptors in the retina and/or choroid in posterior segment sections of postmortem human eyes.

These images were generated using the same radioligands as described in Figure 10. The pseudo-color coding is the same as in Figure 10. (A) Total and non-specific binding of [3H]-PGF2α to FP-receptors. (B) Total and non-specific binding of [3H]-PGE1 to EP-receptors. (C) [3H]-BW828C binding (total and non-specific) to DP-receptors. The figures were adapted and modified from Sharif et al. (1999, 2002, 2004). CHO: Choroid; RET: Retina.

Ocular Allergies

It is well known that the major mast cell mediator culprit responsible for the intense itching and ocular surface (conjunctiva and cornea) redness is histamine, and H1-antagonists with or without mast cell stabilizing properties treat such conditions (see for review Sharif, 2020). However, as mast cells also release additional chemicals including PGD, and PGE, depending on the instigating allergen, it was thought that these PGs may be also involved in causing the allergic conjunctivitis (AC). PGD2, by activating DP-receptors, triggers chemotaxis of eosinophils and ocular surface inflammation in AC (Fujishima et al., 2005). However, Ueta et al. (2009, 2011) have shown that activation of EP3-receptor located on conjunctival epithelial cells may be able to blunt the progression of experimental AC. In another study, Guenoun et al. (2005) demonstrated cytoprotective and antioxidative effects of latanoprost and travoprost against the toxicity induced by benzalkonium chloride in isolated human conjunctival epithelial cells.

Figure 12 | Functional responses to various FP-receptor agonist PG free acids and their relative potencies in isolated human trabecular meshwork (h-TM) cells.

The concentration-response features for FP-receptor agonist compounds that exhibit full agonist and partial agonist properties in an [3H]-inositol phosphates accumulation assay system using hTM cells. The relative functional potencies (EC50 values, nM) derived from the experiments described in (A) are tabulated in (B). The inset (C) depicts the ability of travoprost free acid to stimulate the mobilization of intracellular Ca2+ by activating the FP-receptors present on h-TM cells. The figures and tables were adapted and modified from Sharif et al. (2003a). EC50: Effective concentration that induces 50% of the maximum response possible; IPs: inositol phosphates; Max: maximum; NS: not significant; PG: prostaglandin; RFU: relative fluorescence unit.

Figure 13 | The ability of travoprost free acid to activate functional FP-receptors on human ciliary muscle (h-CM) cells.

Isolated and cultured hCM cells exposed to travoprost free acid (AL-5848) responded by mobilizing intracellular Ca2+ (A) and subsequently stimulating the synthesis and release of matrix metalloproteinase-3 (MMP-3) (B). The figures were adapted and modified from Sharif et al. (2003b). PG: Prostaglandin; Time (S): time in seconds.
Dry Eye Disease
Since the ocular surface is exposed to the environment, it is bombarded with particles, allergens, and sunlight. This causes the tear-mucus components associated with sunlight damage corneal, lens trabecular meshwork, and retinal cells through the generation of reactive oxygen species and thus through oxidative stress. The dryness of the ocular surface is characterized by the feeling of itchiness, foreign-body sensation, and mild to moderate pain (Pflugfelder and de Paiva, 2017). The etiology of dry eye disease (DED) and the related Sjögren’s syndrome is still poorly understood but can be caused by a decrease in circulating female hormones, pollution, reduced blinking, and diseases of the meibomian and lacrimal glands (Clayton, 2018). The latter results in reduced reduction and secretion of natural tears and associated lipids and proteins such as mucins. The only current treatments for DED encompass t.0. dosing with artificial tears, tear secretagogues like diquafosol (a purine receptor agonist), cyclosporin, and an integrin agonist (Lollett and Galicia, 2018). Even though DED is considered to be an inflammatory-based disorder, there is no apparent compelling data that supports the involvement of PGs. However, evidence has accumulated that supports the potential beneficial role of dietary PUFA’s (Figure 2) in reducing some symptoms of DED via limiting oxidative stress (Zhu et al., 2014).

Ocular Inflammation/Pain
Release of endogenous PGs, mainly PGE2, and perhaps PGF2α during eye trauma, inflammation of the anterior and posterior chambers of the eye (uveitis) (Battacherjee and Coles, 1977), and during surgical procedures (e.g., cataract removal; corneal transplants; LASIK procedures) is well documented (Johansen et al., 1987). PGs and PG-inhibitors are prescribed for oral and t.o. administration to cure the production of these PGs and thus reduce ocular inflammation, edema, and pain (Chen et al., 1997; Jacobs, 2017). As COX-inhibitors such as indomethacin, diclofenac, and flurbiprofen are effective therapeutic drugs, there has not been much research performed in determining the potential utility of PG-receptor antagonists in combating ocular pain and inflammation. However, since many EP-receptor-sub-type selective antagonists are now available, these should be evaluated for possible ocular nociceptive efficacy (Bhows at al., 2007; Ganesh, 2014; Rojas et al., 2021).

Optic Neuritis
Spontaneous inflammation, edema, and pain associated with optic nerve components can be initiated by many factors including endogenously released PGs such as PGE2. This normally resolves by itself over 10–14-days but in severe cases requires prescribed for oral and t.o. administration to treat this condition to reduce the potential severity and duration of the ailment. Additional research is needed to determine whether dietary supplementation of PUFA’s and various PG receptor antagonists can impart benefits to patients with optic neuritis.

Myopia
The most prevalent and burdensome refractive eye disorder is myopia (near-sightedness). This ocular defect affects billions of people worldwide and starts in children of school-age (Resnikoff et al., 2019). Family history and environmental factors such as reduced time spent outdoors and time with near work such as reading increases the risk and severity of myopia. Essentially the eye globe is enlarged and elongated such that the light reaching the back of the eye is focused in front of the retina, thereby making the distant images appear blurred to the patient. Several studies have focused on the role of myopic patients are prone to headaches/eye strain and can be victims of retinal detachment, cataracts and closed-angle glaucoma, and potentially pigmentary glaucoma (Resnikoff et al., 2019). The underlying pathology causing the increased axial length of the eyeball is unknown but the signs and symptoms of myopia can be overcome by increasing exposure to sunlight, corrective spectacles, and contact lenses, and via topical eyedrop therapies that contain the muscarinic receptor antagonist atropine which has some mydriatic and other side-effects.

In search for better and safer anti-myopia drugs, two reports described the beneficial effects of FP-receptor agonist analogs latanoprost, dosed topical ocularly (El-Nimri and Wildsoet, 2018), and PGF2α dosed peribulbarly (Yang et al., 2018). Since this improvement in axial length and other features of form-deprivation myopia in the guinea pig model induced by FP receptor agonists was blocked by prior treatment with AL-8810 (Griffin et al., 1999; Sharif and Klimko, 2019), Yang et al. (2018) concluded that the beneficial effect was mediated by FP-receptors. An earlier study using form deprivation in chicks was blocked by prior treatment with AL-8810 (Griffin et al., 1999; Sharif and Klimko, 2019). These reports suggested that FP-R antagonists may have potential clinical utility as anti-angiogenic drugs but such findings need to be confirmed and extended. Of course, combination therapy or multi-pharmacophoric drugs exhibiting simultaneous protective effects via inhibiting multiple PG receptors are also valid approaches to combating ocular diseases such as pathological neovascularization and uveitis. This may be even more important for patients who become recalcitrants to the standard of care anti-VEGF treatments.

Wet Age-Related Macular Degeneration and Diabetic Retinopathy
These ocular diseases primarily impact the back of the eye and in particular the retina and the associated blood vessels. While there may be a small component of the edema and neovascularization that is attributable to elevated levels of PGs, the major culprit here is vascular endothelial growth factor (VEGF). Accordingly, intravitreally delivered anti-VEGF biologics are the current standard of care for these diseases. However, aberrant neovascularization appears to involve various interactions between vascular and ocular tissues. For instance, microvascular and retinal Muller glial cells under ischemic/hypoxic conditions as encountered in oxygen-induced retinopathy of prematurity (Barnett et al., 2010; Hu et al., 2017). Additionally, Savage et al. (2011) showed that latanoprost, a selective FP-R agonist, caused a significant increase in PGE2 from isolated Muller cells and increased proliferation of human retinal microvascular endothelial cells, and these actions were blocked by AL-8810, an FP-R antagonist (Griffin et al., 1999; Sharif and Klimko, 2019). Figure 8B). These results suggested that FP-R antagonists may have potential clinical utility as anti-angiogenic drugs but such findings need to be confirmed and extended. Of course, combination therapy or multi-pharmacophoric drugs exhibiting simultaneous protective effects via inhibiting multiple PG receptors are also valid approaches to combating ocular diseases such as pathological neovascularization and uveitis. This may be even more important for patients who become recalcitrants to the standard of care anti-VEGF treatments.

Some recent studies support the role of PUFA’s as protective agents against choroidal neovascularization (CNV) in models of wet AMD (Gong et al., 2016). These findings have demonstrated that inhibition of cytochrome 450 2C (CYP2C) activity by montelukast in a mouse model O2-induced retinopathy and laser-induced CNV added to the cytoprotective effects of ω-3 long-chain PUFA’s on retinal neovascularization and CNV by 30% and 20%, respectively. Additionally, montelukast reduced retinal neovascularization and in CNV by 20% and 30%, respectively. Of course, combination therapy or multi-pharmacophoric drugs exhibiting simultaneous protective effects via inhibiting multiple PG receptors are also valid approaches to combating ocular diseases such as pathological neovascularization and uveitis. This may be even more important for patients who become recalcitrants to the standard of care anti-VEGF treatments.

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applied FP-R PG agonist analogs (e.g., latanoprost, travoprost, bimatoprost, and tafluprost) effectively reduce IOP by promoting drainage of the AQH through the newly created and/or expanded spaces between ciliary muscle bundles and the sclera (uveoscleral pathway) and also the release of the TM/SC pathways (Figure 14A).

The mechanism of action of these FP-R agonists involved the release of matrix metalloproteinases that act on the extracellular matrix (ECM) ECM that blocks the TM/SC drainage system. While FP-R agonist PG analog drugs are now first-line treatment options for treating OHT (Weinreb et al., 2016a, b), other classes of PGs have also shown efficacy in animal models of OHT/POAG (e.g., DP, EP, FP, FP/EP, and TP receptor agonists), and in OHT/POAG patients (DP-R agonist [AL-6598; Helberg et al., 2007; Sharif et al., 2004], EP-R agonists [DE-177, omedenopag isopropyl (Kirihara et al., 2018a, b)], and FP/EP receptor agonist [ONO-9504 or sepoprost; Suto et al., 2015]). A conjugated PG analag (latanoprostene bunod; Cavet and DeCory, 2014) and DE-177 (Morgan et al., 2016) were recently approved for the clinical management of the latter ocular disease. This drug lowers IOP by releasing nitric oxide in the ANC to relax TM/SC cells and by co-releasing latanoprost that stimulates egress of AQH through the uveoscleral pathway and conventional TM pathway (Weinreb et al., 2016b; Cavet and DeCory, 2018).

As noted above, being avascular, the cells and tissues in the ANC of the eye are dependent on the AQH to supply them with glucose, O₂, antimicrobial proteins, amino acids required for protein synthesis, anti-oxidants like ascorbic acid and glutathione, and a whole range of vital minerals and trace elements for efficient intracellular, membrane-bound and mitochondrial enzyme activities. When the AQH drainage is restricted the ambient AQH is increased, and this leads to the accumulation of aqueous humor in the eye. In addition, the increased AQH is associated with increased intraocular pressure (IOP) in the ANC, which can be deleteriously affected by aberrant ECM deposits within the angular space of the eye, and also of RGCs in the retina (Thomas et al., 2000) that deleteriously affects vision (Ashworth-Briggs et al., 2015; Cabrerizo et al., 2015). The levels of AQH with AQH changes to create such an unhealthy environment within the ANC that reduces the ability of TM cells, for instance, to release matrix metalloproteinases and to phagocytose the offending materials in the AQH (Ashworth-Briggs et al., 2015; Cabrerizo et al., 2017; Adav et al., 2013; Hubens et al., 2020). Thus, FP-R agonist analogs not only help lower and control IOP over 24-hours by removing excess AQH from the ANC of the eye, but their particular mechanism of action also helps replenish the fluid in the ANC with fresh AQH and thus they promote better health in the eye. TM cells. The latter feature is important since healthy and well-nourished TM/SC cells are far better at phagocytizing debris (autophagy; Porter et al., 2015) and any foreign materials in the ANC than sick ones and thus prevent future occlusion and damage of the TM/SC is achieved.

As mentioned above, since TM/SC/ciliary muscle cells are negatively and strongly induced Nur77 expression, an orphan nuclear receptor that requires an elevation of intracellular and extracellular Ca²⁺ concentrations of autotaxin, the enzyme that converts different types of extracellular lipids (e.g., diacylglycerol, lysophosphatidyl choline) to the release of LPA, and most probably selective antagonists of LPA receptors (Figure 15A), and the levels of LPA and lysophosphatidyl choline were substantially elevated in patients with normotensive glaucoma, POAG, secondary open-angle glaucoma, and exfoliation glaucoma (Nagano et al., 2019; Figure 16A–C). Inhibitors of autotaxin dosed intravitreally (e.g., 532826; Iyer et al., 2012) or t.o. (Nagano et al., 2019) in animals lowered IOP (Figures 15B, and 16D, E). The differences in the magnitude of the ocular hypertensive responses induced by the two autotaxin inhibitors are related to their potencies and due to their different routes of administration. Nevertheless, reducing the intraocular concentrations of the LPA, and most probably selective antagonists of LPA receptors (Figure 15A), results in beneficial outcomes in terms of enhancing AQH drainage and replenishing the ANC’s AQH with freshly produced fluid from the ciliary body thereby keeping the tissues surrounding the eye well nourished with nutrient-rich blood. Whether autotaxin inhibitors and/or LPA antagonists have similar direct or indirect protective effects in the retina/choroid remains to be determined.

Neuroprotective Effects of PGs

During chronic OHT the elevated IOP in the ANC of the eye is constantly increased and distention at the back of the eye inducing local inflammation at the optic nerve head. Over time, this damages the RGC axons and eventually kills the RGCs via multiple factors and pathways (Figure 14B), resulting in visual impairment (Weinreb et al., 2014). Over many years, the patient loses peripheral vision and can become blind if left untreated. To preserve eyesight, OHT/glaucoma patients receive IOP-lowering topical eyedrops. Even though this slows down the speed of visual impairment, the patients continue to progress towards serious visual loss. Several recent studies (Weinreb et al., 2008) have clearly demonstrated that the AQH contains a normal similarly progressing towards debilitating eyesight and visual field defects. Therefore, drugs that can directly or indirectly preserve RGCS and their axons are eagerly being sought.

Regarding the potentially damaging effects of ET at the TM-level, Thieme et al. (2006) demonstrated that PGF₂α and fluoroprost blocked the ET-induced increase in IOP in the TM. Whether autotaxin inhibitors and/or LPA antagonists have similar direct or indirect protective effects in the retina/choroid remains to be determined.

Figure 14 Aqueous humor dynamics in the human eye and the multiplicity of factors involved in the death of retinal ganglion cells and their axons due to elevated IOP.

(A) The generation of AQH by the ciliary body non-pigmented ciliary epithelial cells, its perfusion path through the ANC of the eye and its drainage via the conventional outflow pathway (trabecular meshwork and Schlemm’s canal), and the uveoscleral outflow pathway in a human eye (adapted and modified from Sharif, 2020). (B) The multitude of factors and processes involved in the death of RGCs (and their axons) and thalamic and visual cortex structural-functional damage (gliogenesis and optic neuropathy (adapted and modified from Calkins and Horner, 2012). ANC: Anterior chamber; AQH: aqueous humor; C: complement; NDT: nucleus of optic tract; OP: optic pretectal; PPT: posterior pretectal; RGC: retinal ganglion cell; SC: Schlemm’s canal; SCN: suprachiasmatid nucleus; TM: trabecular meshwork; UVSP: uveoscleral pathway.

Review

Figure 15A

*Figure 15AR**
Review

In various animal models of OHT/POAG disease involving either NMDA-induced neurotoxicity, optic nerve crush/axotomy, or ischemia-reperfusion procedures, intravitreally delivered latanoprost (Kudo et al., 2006; Hernandez et al., 2006) and tramiprost (Sperduto et al., 2006) and unoprostone (Melamed et al., 2004) demonstrated RGC protective activity in rats and rabbits. As mentioned above, tafluprost also enhanced RGC survival in the optic nerve crush model (Kanamori et al., 2009). In a similar vein, various FP-R agonist PGs (including tafluprost, travoprost, and latanoprost) have been shown to enhance ocular blood-flow at or close to the optic nerve head in rabbits/rats (Inan et al., 2004; Ohashi et al., 2008; Akashi et al., 2010; Kurushima et al., 2010) and in human subjects (Cardascia et al., 2003; Koz et al., 2007; Alagona et al., 2008; Giannino et al., 2016). This is regarded as a beneficial effect of these PGs since low blood perfusion pressure at the optic nerve head, along with other ocular vascular abnormalities, is associated with POAG development (Flammer et al., 2013; Pasquale, 2016). One culprit responsible for this low IOP in ischemia/hypoxic retina is ET, a well-known vasoconstrictor peptide that is elevated in glaucomatous conditions in animal models of OHT and OHT/POAG patients (Chorzinski et al., 2012). ET mediates these detrimental effects by enhancing intracellular calcium ([Ca$^{2+}$]i) and contractile activity of smooth vessels, and in case of individual cells like RGCs, its toxic effect results from Ca$^{2+}$-overloading (Prasanna et al., 2011; Stankowska et al., 2017). As such, tafluprost protected retinal injury after intravitreal injection of EJ-1 (Nagata et al., 2014). In another study, Kurushima et al. (2010) showed that tafluprost, latanoprost, and travoprost concentration-dependently relaxed ET-1-induced ciliary artery in vitro indicating that indeed these FP-R agonists may directly enhance ocular blood-flow in vivo by counter-acting any locally produced ET or other vasoconstrictor substances.

Additional therapeutic approaches that have shown promise to stabilize and rescue apoptotic or injured RGCs include the use of PGs to ameliorate and release of endogenous neuroprotective factors by different pharmaceutical classes of agents. These have included alpha-2-adrenergic agonists such as brimonidine (Gao et al., 2001) and certain beta-adrenergic antagonists (e.g., betaxolol; Wood et al., 2001), where in vitro and in vivo efficacy was observed. Likewise, exogenously delivered cilostat neuroprotective factor, brain-derived neuroprotective factor, or gene therapy delivery brain-derived neuroprotective factor gene-transfected RGCs successfully provided RGC neuroprotection in vivo. Both cilostat and its structural analogues have demonstrated neuroprotection ex vivo in rodent models of glaucoma, and these findings have been expanded to humans with glaucoma (He et al., 2018). Thus, in a comprehensive comparative series of studies, Yamagishi et al. (2011) found that 100 nM free acids of tafluprost, unoprostone and travoprost free acid protected rat RGCs from glutamate-induced toxicity and serum-deprivation insults, and it exposed to glutamate-induced toxicity and serum-deprivation insults, and it released of endogenous neurotrophic factors by different pharmacological classes of agents. These have included alpha-2-adrenergic agonists such as brimonidine (Gao et al., 2001) and certain beta-adrenergic antagonists (e.g., betaxolol; Wood et al., 2001), where in vitro and in vivo efficacy was observed. Likewise, exogenously delivered cilostat neuroprotective factor, brain-derived neuroprotective factor, or gene therapy delivery brain-derived neuroprotective factor gene-transfected RGCs successfully provided RGC neuroprotection in vivo. Both cilostat and its structural analogues have demonstrated neuroprotection ex vivo in rodent models of glaucoma, and these findings have been expanded to humans with glaucoma (He et al., 2018).

**Conclusions**

It should be apparent from the above treatise that PGs and their receptors are intimately involved in many homeostatic and thus beneficial actions in the eye. In contrast, released PGs are known to produce detrimental effects due to their pro-inflammatory properties. This pluripotency of PGs makes it hard to always ascribe destructive or neuroprotective features of these ubiquitous endogenous mediators. Therefore, it is important to have both PGs and their therapeutic potential in mind when attempting to manage GON.

**Table 2**

| Direct neuroprotective effects of PG agonists have been demonstrated using isolated rat primary RGCs subjected to a variety of insults presumed to occur in vivo at the back of the eye in chronic OHT, POAG, and other forms of glaucoma (He et al., 2018). Thus, in a comprehensive comparative series of studies, Yamagishi et al. (2011) found that 100 nM free acids of tafluprost, latanoprost, and bimatoprost significantly (P < 0.001) protected rat RGC cells from glutamate-induced and hypoxia-induced apoptotic cell death. Interestingly, PGF$_2$α, unoprostone and travoprost free acids were marginally protective. The RGC-rescuing effects of latanoprost free acid in the above studies confirmed earlier reports by Drago et al. (2001) using both retinal cell-based assays involving glutamate-toxicity and hypoxia-reoxygenation and an in vivo rat model of ischemia-reperfusion. Likewise, latanoprost increased the survival of retinal neuro-glial cells by inhibiting caspase-3 (Nakanishi et al., 2006). Furthermore, latanoprost acid derived from a hydrogen sulfide-releasing agent conjugated to latanoprost free acid protected rat photoreceptors in a cell line exposed to oxidative stress and protected RGCs in the rat OHT model of POAG (Osborne et al., 2010). Interestingly, tafluprost was also shown to increase photoreceptor survival in the cell-line exposed to glutamate-induced toxicity and serum-deprivation insults, and it exhibited neuroprotective properties in an optic nerve crush model of POAG/ OHT (Kanamori et al., 2009). Similarly, latanoprost enhanced the growth of “neurites” in the same photoreceptor cell line (Zheng et al., 2011). Moreover, an EP$_2$ receptor agonist, ONO-ACE-259-01 injected intravitreally abolished the neurotoxic effects of NMDA on RGCs (Mori et al., 2009). All these latter beneficial actions of EP- and FP-receptor agonists in vitro and in vivo are mediated by the receptors located in the retina and choroid (Figure 11).
