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THERAPEUTIC TARGETS FOR GLAUCOMA

L.A. Sorbera, J. Aravamudan, C. Dulsat and E. Rosa

Thomson Reuters, Barcelona, Spain

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SUMMARY

Glaucoma is a group of progressive optic neuropathies that involves the death of retinal ganglion cells, the consequent deformation of the optic nerve head and a progressive reduction in the visual field. The disease can be associated with elevated intraocular pressure (IOP) due to accumulation of aqueous humor. The buildup of aqueous fluid compresses the nerve fibers of the optic nerve, leading to damage and loss of vision. There is no cure for glaucoma, although the condition can be managed through reduction of IOP. In general, existing pharmacotherapy consists of improving the flow or reducing the production of intraocular fluid. Available agents include miotics, β-blockers, carbonic anhydrase inhibitors, prostaglandin analogues and α_2-adrenoceptor agonists. However, the search continues for more effective treatment strategies for glaucoma, with investigation focusing on identifying novel targets for therapeutic intervention. This article presents those drug targets that are currently under active investigation for the treatment of glaucoma.

INTRODUCTION

Glaucoma refers to a heterogeneous group of progressive optic neuropathies characterized by the death of retinal ganglion cells. This causes the deformation of the optic nerve head and a progressive reduction in the visual field. The disease is often associated with elevated intraocular pressure (IOP). Under normal conditions, aqueous humor produced by the ciliary body circulates constantly though the healthy eye to maintain IOP and the shape of the eye. After nourishing the cornea and the lens, the fluid flows out through the trabecular meshwork (TM), an active filter which, through contractile activity, can control changes in cell volume and the cytoskeleton, as well as interactions with the extracellular matrix and aqueous humor outflow. Elevated IOP is due to the accumulation of intraocular aqueous fluid, which consequently compresses the nerve fibers of the optic nerve. Chronically elevated IOP can lead to morphological and physiological changes in both the optic nerve head and retina, which result in progressive optic nerve damage and consequent vision loss (1-5).

Glaucoma is the leading cause of blindness in the U.S. The global prevalence of glaucoma has been predicted to be 60.5 million people worldwide for the year 2010, with an increase to 79.6 million estimated for 2020. There are four major forms of glaucoma: open-angle, angle-closure (also known as closed-angle), congenital and secondary. In open-angle glaucoma (OAG), the aqueous humor drains too slowly through the periphery of the anterior chamber, creating a chronic rise in fluid pressure inside the eye; it is referred to as open-angle because the anterior chamber is open to aqueous humor outflow. The slow drainage of aqueous humor through the TM causes fluid pressure to build up, often unnoticeably. OAG may be primary or secondary in nature and the most common form of secondary OAG is pseudoexfoliation syndrome (1, 6-11).

To date, there is no cure for glaucoma, although further damage and blindness can be prevented through early detection and treatment. IOP is the only contributing factor that can be clinically modified in this condition, and thus, the primary objective in treating glaucoma is to reduce IOP in order to prevent additional optic nerve damage and preserve remaining vision. Lowering of IOP can be achieved using pharmacotherapy, although laser surgery (laser trabeculoplasty), conventional surgery or glaucoma filtering surgery may be performed if drugs alone are not effective. Antiglaucoma drugs improve the flow of intraocular fluid or decrease the amount of fluid produced by the eye. The resulting reduction in IOP protects the optic nerve from damage, thereby preventing further glaucomatous progression. The most frequently used drug classes to date are miotics, β-blockers, carbonic anhydrase inhibitors, prostaglandin analogues and α_2-adrenoceptor agonists. Miotic agents produce constriction of the ciliary muscle, opening the drainage channels in the TM. Carbonic anhydrase inhibitors and β-blockers decrease aqueous humor production, and prostaglandin analogues increase the uveoscleral outflow of aqueous humor. α_2-Adrenoceptor agonists both decrease aqueous humor production and increase uveoscleral outflow (1, 4, 5, 12, 13).

The search for effective treatment strategies for glaucoma continues, with research focusing on the identification of novel targets for drug development. Those targets currently under active investigation are discussed below (see Fig. 1). Table I provides a selection of products under active development for each target and Table II includes selected patents.

Correspondence: L.A. Sorbera, Thomson Reuters, Provença 388, 08025 Barcelona, Spain. E-mail: lisa.sorbera@thomsonreuters.com.

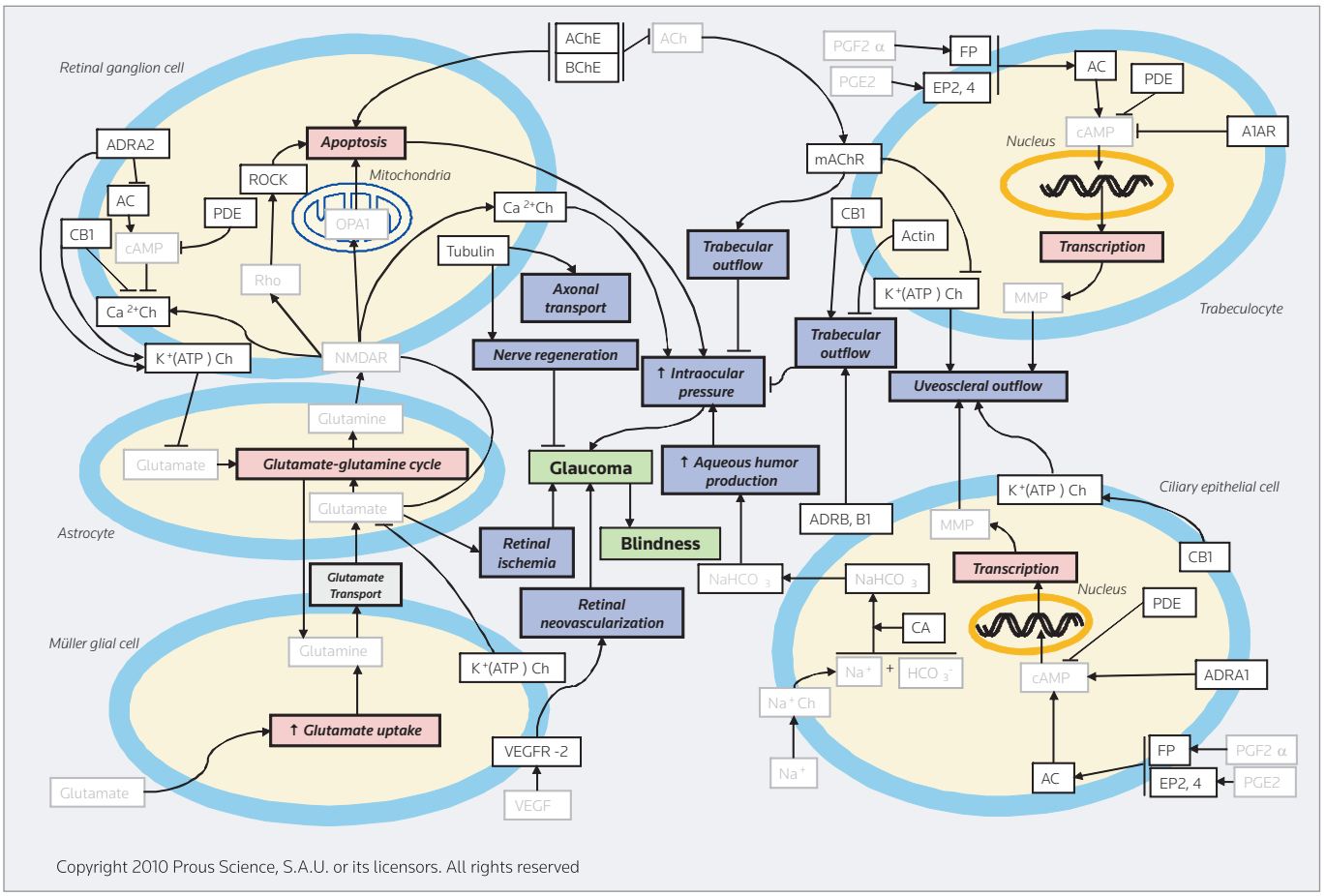

Figure 1. Glaucoma targetscape. A diagram showing an overall cellular and molecular landscape or comprehensive network of connections among the current therapeutic targets for the treatment of glaucoma and their biological actions. Gray or lighter symbols are targets that are not validated (i.e., targets not associated with a product that is currently under active development for glaucoma). Abbreviations: A1AR, adenosine A_1 receptor; AC, adenylate cyclase; AChE, acetylcholinesterase; ADRA1, α_1-adrenoceptor; ADRA2, α_2-adrenoceptor; ADRB, β-adrenoceptor; BChE, butyrylcholinesterase; CA, carbonic anhydrase; Ca^{2+} Ch, calcium channel (nonspecified subtype); CB1, cannabionoid CB_1 receptor; EP2, prostanoid EP_2 receptor; EP4, prostanoid EP_4 receptor; FP, prostanoid FP receptor; K+(ATP) Ch, potassium channel; mAChR, muscarinic acetylcholine receptor; PDE, cAMP phosphodiesterase (nonspecified subtype); ROCK, Rho-associated protein kinase; VEGFR-2, vascular endothelial growth factor receptor 2.

TARGETS

Acetylcholinesterase (AChE) and butyrylcholinesterase (BChE)

AChE (EC 3.1.1.7) and BChE (EC 3.1.1.8) are members of the cholinesterase family of enzymes that catalyze the hydrolysis of acetylcholine (ACh). AChE/BChE inhibitors are hypotensive agents that can lower IOP and therefore may be effective in the treatment of glaucoma (14-17).

Actin

Actin is a globular, highly conserved protein (about 42 kDa). It is the monomeric subunit of the microfilaments (a major component of the cytoskeleton) and thin filaments (component of the contractile apparatus in muscle cells). Actin is involved in muscle contraction, cell motility, cell division and cytokinesis, vesicle and organelle movement, cell signaling and the establishment and maintenance of cell junctions and cell shape. The three groups of actin isoforms identified are: alpha, found in muscle tissue; and beta and gamma, which are both found in most cell types where they mediate cell shape, volume, contractility and adhesion. The actomyosin system plays an important role in mediating trabecular outflow resistance via regulation of the dimensions or direction of flow pathways and the amount and composition of the extracellular matrix. Studies have shown that in glaucomatous eyes, F-actin arrangement in the inner wall and juxtacanalicular connective tissue cells of the outflow system may be more disordered, and F-actin tangles among the stress fibers may be more abundant. Actin-disrupting agents could be effective in altering trabecular fluid outflow and would therefore be effective in the treatment of ocular hypertension and glaucoma (18-20).

Adenosine A_1 receptor

The adenosine A_1 receptor is one of four distinct G protein-coupled receptor (GPCR) subtypes (A_1, A_{2A}, A_{2B} and A_3) that mediate adenosine action. It is coupled to $G_{i/o}$ and activation causes inhibition of adenylate cyclase (AC) and consequent decreases in intracellular

Table I. *Selected targets and products launched or being activity investigated for glaucoma (from Thomson Reuters Integrity℠).*

Target	Product	Source	Phase
Acetylcholinesterase	Physostigmine salicylate	Forest	L-1949
Actin (nonspecified subtype)	INS-115644	Inspire Pharmaceuticals	I
Adenosine A_1 receptor	INO-8875	Inotek	I/II
Adenylate cyclase (nonspecified subtype)	Colforsin	Sabinsa/Sami Labs	Reg-2006
α-Adrenoceptor (nonspecified subtype)	Nipradilol	Kowa	L-1999
α_1-Adrenoceptor	Bunazosin hydrochloride	Santen	L-2001
α_2-Adrenoceptor (nonspecified subtype)	Dapiprazole hydrochloride	Angelini	L-1986
	Apraclonidine hydrochloride	Alcon	L-1988
	Brimonidine tartrate	Allergan	L-1998
β-Adrenoceptor (nonspecified subtype)	Carteolol hydrochloride	Otsuka Pharmaceutical/Senju	L-1984
	Befunolol hydrochloride	Kaken	L-1984
	Metipranolol	Bausch & Lomb	L-1985
	Nipradilol	Kowa	L-1999
β_1-Adrenoceptor	Timolol maleate	Santen	L-1981
	OT-730	QLT	I/II
Calcium channels (nonspecified)	Lomerizine hydrochloride	Santen	II
cAMP phosphodiesterase (nonspecified subtype)	Moxaverine hydrochloride	Medizinische Universitaet Wien	II
Cannabinoid CB_1 receptor	CXB-006	CeNeRx BioPharma	Preclinical
Carbonic anhydrases (nonspecfied subtype)	Brinzolamide	Alcon	L-1998
K_{ATP} channel (nonspecified subtype)	KR-31378	Danube Pharmaceuticals	II
Muscarinic acetylcholine receptor (nonspecified subtype)	Pilocarpine hydrochloride	Alcon	L-1965
	AC-262271	Acadia	I
Prostanoid EP_2 receptor	Taprenepag isopropyl	Pfizer	II
Prostanoid EP_4 receptor	PF-04475270	Pfizer	Preclinical
Prostanoid FP receptor	Latanoprost	Pfizer	L-1996
	Travoprost	Alcon	L-2001
	AR-102	Aerie Pharmaceuticals	II
Rho-associated protein kinase (ROCK) (nonspecified)	DE-104	Santen/Ube	II
	K-115	Kowa	II
	Y-39983	Senju	II
	AR-12286	Aerie Pharmaceuticals	II
	INS-117548	Inspire Pharmaceuticals	I
	ATS-907	Altheos	Preclinical
Tubulin (nonspecified subtype)	Fosbretabulin disodium	Oxigene	Preclinical
Vascular endothelial growth factor receptor VEGFR-2 (FLK-1)	Epigallocatechin gallate	Universita Cattolica del Sacro Cuore	I/II

3′,5′-cyclic AMP (cAMP) concentration. Studies have shown that agonists of the adenosine A_1 receptor can decrease elevated IOP by enhancing trabecular fluid outflow. Thus, adenosine A_1 receptor agonists may be effective in the treatment of glaucoma (21, 22).

Adenylate cyclase (AC)

AC is a membrane-bound lyase (EC 4.6.1.1), also known as adenylyl cyclase, that converts ATP to cAMP and pyrophosphate. It can be activated or inhibited by G proteins which are coupled to membrane receptors and thus can respond to hormonal or other stimuli. cAMP formed following activation of AC acts as a second messenger by interacting with and regulating other proteins (e.g., protein kinase A [PKA], cyclic nucleotide-gated ion channels). Forskolin and other class-specific substrates can also activate AC. For example, isoforms I, III and VIII are also stimulated by Ca^{2+}/calmodulin and isoforms V and VI are inhibited by Ca^{2+} in a calmodulin-independent manner. Activation of AC appears to affect outflow facility, mediated by cAMP, which is independent of muscle contraction, and may therefore be an effective treatment for glaucoma (21, 23).

α_1-Adrenoceptor

The α_1-adrenoceptor is a subtype of α-adrenoceptor that signals via $G_{p/q}$ proteins following binding of neurotransmitters such as epinephrine and norepinephrine. Signaling involves phospholipase C (PLC)-mediated cleavage of phosphatidylinositol 4,5-bisphosphate (PIP_2), resulting in an increase in inositol triphosphate (IP_3) and diacylglycerol (DAG). DAG interacts with calcium channels of the endoplasmic and sarcoplasmic reticulum, increasing intracellular calcium release. Activation of the α_1-adrenoceptor induces smooth muscle contraction and causes vasoconstriction and bronchocon-

Table II. *Selected patents for targets being validated for glaucoma (from ThomsonReuters Integrity^{SM}).*

Target	Patent	Source	Phase
Acetylcholinesterase	WO 2008073452	Reviva	Biological testing
α_2-Adrenoceptor	WO 2007005177	Allergan	Biological testing
	WO 2007090793	NicOx/Pfizer	Biological testing
Carbonic anhydrase	WO 2007054580	Solvay	Biological testing
	WO 2007065948	Solvay	Biological testing
	WO 2008017932	Pfizer	Biological testing
	WO 2008075148	Pfizer	Biological testing
	WO 2008075152	Pfizer	Biological testing
	WO 2008120099	Pfizer	Biological testing
	WO 2008130332	Unimed Pharma	Biological testing
	WO 2009007814	Pfizer	Biological testing
Prostanoid EP_2 receptor	WO 2007017687	Asterand UK	Biological testing
	WO 2007115020	Allergan	Biological testing
	WO 2007130902	Allergan	Biological testing
	WO 2007131012	Allergan	Biological testing
	WO 2008008700	Allergan	Biological testing
	WO 2008008701	Allergan	Biological testing
	WO 2008008718	Allergan	Biological testing
	WO 2008015517	Pfizer	Biological testing/Phase II
	WO 2008021933	Allergan	Biological testing
	WO 2008064039	Allergan	Biological testing
	WO 2008073752	Allergan	Biological testing
	WO 2008091810	Allergan	Biological testing
	WO 2008091818	Allergan	Biological testing
	WO 2008091860	Allergan	Biological testing
	WO 2008094912	Allergan	Biological testing
	WO 2009055289	Allergan	Biological testing
	WO 2009061811	Allergan	Biological testing
	WO 2009111322	Allergan	Biological testing
	WO 2009111417	Allergan	Biological testing
	WO 2009117465	Allergan	Biological testing
	WO 2009132085	Allergan	Biological testing
	WO 2009132097	Allergan	Biological testing
	WO 2009136281	NicOx	Biological testing
	WO 2009142967	Allergan	Biological testing
	WO 2009146255	Allergan	Biological testing
	WO 2010022033	Allergan	Biological testing
Prostanoid EP_4 receptor	WO 2007014454	Merck Frosst Canada	Biological testing
	WO 2007014462	Merck Frosst Canada	Biological testing
	WO 2008017164	Merck Frosst Canada	Biological testing/Preclinical
Prostanoid FP receptor	WO 2009004990	Kyowa Hakko Kirin	Biological testing
Rho-associated protein kinase (ROCK)	WO 2007026664	Asahi Kasei	Biological testing
	WO 2007065916	Organon	Biological testing
	WO 2007142323	Ube/Santen	Biological testing
	WO 2008020081	Organon	Biological testing
	WO 2008036540	Boehringer Ingelheim	Biological testing/Preclinical
	WO 2008049919	Devgen	Biological testing
	WO 2008077550	sanofi-aventis	Biological testing
	WO 2008077551	sanofi-aventis	Biological testing
	WO 2008077552	sanofi-aventis	Biological testing
	WO 2008077553	sanofi-aventis	Biological testing
	WO 2008077554	sanofi-aventis	Biological testing
	WO 2008077555	sanofi-aventis	Biological testing
	WO 2008077556	sanofi-aventis	Biological testing
	WO 2008086047	Boehringer Ingelheim	Biological testing
	WO 2008105058	Asahi Kasei	Biological testing
	WO 2009004792	Asahi Kasei	Biological testing
	WO 2009156099	sanofi-aventis	Biological testing
	WO 2009156100	sanofi-aventis	Biological testing
	WO 2010032875	Astellas Pharma	Biological testing

striction. Together with β-adrenoceptors, the α_1-adrenoceptor is involved in the production of aqueous humor, and thus regulation of IOP. α_1-Adrenoceptor antagonists may therefore be effective in the treatment of ocular hypertension and glaucoma (24, 25).

α_2-Adrenoceptor

The α_2-adrenoceptor is a subtype of α-adrenoceptor that mediates the catecholamine-induced inhibition of AC via G_i. It binds both norepinephrine and epinephrine, with slightly higher affinity for the latter neurotransmitter. It also modulates the activity of the NMDA receptor, which may be responsible for the neuroprotective effects seen with α_2-adrenoceptor agonists. Effects of receptor activation include regulation of arterial vasodilatation and vasoconstriction, venous vasoconstriction and smooth muscle contractility. α_2-Adrenoceptor agonists have been shown to protect retinal ganglion cells in animal models of glaucoma and may be effective in the treatment of glaucoma (26-28).

β-Adrenoceptors and β_1-adrenoceptor

β-Adrenoceptors are GPCRs present in effector tissues that bind endogenous catecholamines such as norepinephrine and epinephrine. Three isoforms have been discovered: β_1, β_2 and β_3. While β_1-and β_2-adrenoceptors are widely distributed, the distribution of β_3-adrenoceptors is predominantly in adipocytes. All three isoforms are coupled to G_s proteins, and the β_2-adrenoceptor is also coupled to G_i. Binding to β-adrenoceptors activates AC, which generates cAMP. cAMP in turn activates PKA, which phosphorylates the ryanodine receptor (RyR) on the sarcoplasmic reticulum. Phosphorylation of RyR by the ryanodine receptor initiates the dissociation of FKBP12.6 and phospholamban, which modulate the activity of the Ca^{2+}-ATPase, SERCA (sarco/endoplasmic reticulum). β-Adrenoceptor kinase (β-ARK; EC 2.7.11.15) is also activated upon binding, which phosphorylates the cytoplasmic tail of the receptor, thus decreasing receptor signaling (negative feedback loop). Stimulation of β-adrenoceptors has numerous effects, including vasodilatation, bronchodilatation and smooth muscle relaxation. Stimulation of ocular β-adrenoceptors normally decreases IOP via an increase in aqueous humor production, which causes enhancement of pressure-dependent uveoscleral humoral outflow. However, in glaucoma, drainage of aqueous humor is reduced or blocked, and antagonists would be effective in decreasing IOP and thus an effective treatment for this condition (29-31).

Calcium channels

Calcium channels are pore-forming proteins present in cell membranes that control the flow of ions, thereby establishing the small voltage gradient across the cell membrane. These voltage-gated channels (L-, N-, P/Q-, R- and T-type) are formed as a complex of several different subunits and are prominent throughout the nervous system, where they are responsible for triggering the release of neurotransmitters. Inhibition of calcium channels can improve blood supply to the retina and the optic nerves by enlarging the intraocular blood vessels. This could retard the gradual deterioration of vision associated with glaucoma and macular degeneration. Moreover, secondary optic nerve degeneration, which can occur in response to injury-induced increases in Ca^{2+} influx into neurons and glia accompanied by macrophage infiltration, can be reduced by treatment with calcium channel blockers. In addition, treatment may protect retinal ganglion cells and partially preserve visual function, which may be effective in the management of glaucoma (32-34).

cAMP phosphodiesterase

cAMP phosphodiesterases (PDEs) are a family of PDE isozymes (EC class 3.1.4) that degrade cAMP and cGMP, thereby modulating their respective signal transduction. cAMP PDE isoenzymes are characterized by high affinity for cAMP and poor affinity for cGMP. PDE inhibitors have been shown to increase choroidal blood flow and may therefore be beneficial in the treatment of macular degeneration and glaucoma (35-37).

Cannabinoid CB_1 receptor

The cannabinoid CB_1 receptor is a 7-transmembrane-spanning GPCR, which, together with CB_2, has been identified as the receptor for cannabinoids. The CB_1 receptor is preferentially expressed in the brain, where it mediates the psychoactivity of cannabinoids. High levels of CB_1 receptors are found in the basal ganglia, hippocampus, cerebellum and cortical structures. CB_1 receptors are coupled through the $G_{i/o}$ family of proteins to signal transduction mechanisms that include inhibition of AC and activation of mitogen-activated protein kinase (MAPK). Activation of presynaptic CB_1 receptors inhibits N-type Ca^{2+} channel activity, which in turn reduces excitatory neurotransmitter release to the synaptic cleft, thus allowing the excitatory signals to activate the postsynaptic cell. CB_1 receptor agonists may be effective in the treatment of various CNS-related disorders, including glaucoma, multiple sclerosis and pain, among others (38-40).

Carbonic anhydrases

Carbonic anhydrases are a family of zinc-containing enzymes (EC 4.2.1.1) that catalyze the conversion of CO_2 and H_2O to HCO^{3-} and H^+, respectively, a reaction essential for many physiological processes (e.g., respiration, renal acidification, bone resorption, formation of aqueous humor and cerebral fluid, gastric acid secretion). There are 10 human isoenzymes identified: 3 cytosolic isoenzymes (CA I, II and III), 5 membrane-bound isoenzymes (CA IV, VII, IX, XII and XIV), 1 mitochondrial isoenzyme (CA V) and 1 secreted salivary isoenzyme (CA VI); there are also several related proteins that lack catalytic activity. The isoenzymes facilitate the intracellular diffusion of CO_2 and protons (H^+). Inhibition of carbonic anhydrase effectively reduces fluid production by the eye, thus decreasing IOP, and also aids in the preservation of visual field (41-43).

$K_{ir}6$ channels

$K_{ir}6$ channels are a group of inwardly rectifying potassium channels that are sensitive to ATP. $K_{ir}6.2$ is one such channel that is expressed on pancreatic β-cells and skeletal muscle, and in the heart and brain. These channels are also involved in cytoprotection against ischemic insults and metabolic sensoring in the brain. Studies have shown that $K_{ir}6$ channel activators reduce IOP, exert neuroprotective activity on the optic nerve and prevent ischemic injury-induced ganglion cell loss in glaucoma (44-46).

Muscarinic acetylcholine receptors (mAChRs)

mAChRs are a class of membrane-bound, G protein-coupled, 7-transmembrane-spanning metabotropic receptors that are expressed predominantly within the parasympathetic nervous system. Five subtypes of muscarinic receptors (M_1-M_5) have been described and exert inhibitory and excitatory control over central and peripheral tissues. They inhibit AC and the breakdown of phosphoinositides and modulate potassium channels through the action of G proteins. mAChRs play a role in many physiological functions, including regulation of IOP, and muscarinic agonists have been shown to increase aqueous humor outflow facility in the TM via direct stimulation of ciliary muscle contraction. They have also been shown to exert neuroprotective activity against glutamate cytotoxicity in retinal neurons. mAChR agonists may therefore be effective in the treatment of elevated IOP and glutamate-induced neuronal apoptosis in glaucoma (47-49).

Prostanoid EP_2 receptor

The prostanoid EP_2 receptor is a GPCR that mediates the actions of prostaglandin E_2 (PGE_2) and is characterized by a compact structure when compared to other prostanoid receptors. Mainly, EP_2 receptors couple to G_s and mediate elevations in cAMP concentration, although they also participate in other pathways as well. In glaucoma, EP_2 receptor agonists would increase intracellular cAMP levels and might be effective in lowering IOP and attenuating retinal ganglion cell death (50-53).

Prostanoid FP receptor

The prostanoid FP receptor is the GPCR for prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$). Binding to the receptor activates signaling via phosphatidylinositol calcium second messengers. The receptor plays a role in luteolysis, uterine smooth muscle contraction and modulation of IOP. Agonists may be effective in the treatment of glaucoma (54, 55).

Rho-associated protein kinase (ROCK)

Rho-associated protein kinase (ROCK1 and ROCK2) is a serine/threonine-specific protein kinase involved in the RhoA/Rho-associated kinase signaling pathway which regulates the state of phosphorylation of myosin phosphatase; it is activated by GTP-bound RhoA. ROCK phosphorylates many substrate proteins and controls a wide variety of cellular functions, including smooth muscle contraction and proliferation, angiogenesis and synaptic remodeling. Inhibition of ROCK has been shown to increase local outflow hydrodynamics, thus reducing IOP in glaucoma (56-58).

Tubulin

Tubulins are cytoplasmic proteins that are divided into three classes: α, β and γ. α- And β-tubulins form heterodimers that polymerize into cylindrical microtubule fibers. These microtubule fibers are found in almost all eukaryotic cell types and are involved in mitosis and motility. β-Tubulin binds GTP and hydrolyzes GTP to GDP. This process of hydrolysis is associated with tubulin polymerization and microtubule formation. α-Tubulin also binds GTP, but does not have GTP/GDP hydrolysis activity. However, α-tubulin can be modified by addition of a *C*-terminal tyrosine residue, which affects polymerization rates. Some antimitotic agents act by overstabilizing GDP-bound tubulin in the microtubule, whereas others block microtuble formation and destroy mitotic spindles. Disruption of microtubule formation and consequent arrest of the mitotic process is currently a successful strategy for the treatment of cancer and optic neuropathies, including macular degeneration and glaucoma (59-61).

Vascular endothelial growth factor receptor VEGFR-2 (FLK-1)

VEGFR-2 is a protein-tyrosine kinase receptor that is a kinase insert domain receptor (KDR) belonging to the vascular endothelial growth factor receptor (VEGFR) family. It is a receptor for VEGF-A and VEGF-C and plays a critical role in angiogenesis, regulating the growth and survival of endothelial cells in newly forming vasculature. While VEGFR-2-mediated proliferation of endothelial cells occurs via activation of the phospholipase C PLC-γ and c-Raf/MAP signaling pathways, the phosphatidylinositol 3-kinase (PI3K) and focal adhesion kinase (FAK) pathways are responsible for survival and migrational signaling. The VEGF/VEGFR pathway promotes a network of signaling processes that induce endothelial cell growth, migration and survival from preexisting vasculature and mediates vessel permeability. It also functions as an antiapoptotic factor for newly formed blood vessels, as well as an inducer of the mobilization of endothelial progenitor cells from bone marrow to distant sites. VEGFR-2 inhibitors may be useful for treating eye disorders such as macular degeneration and glaucoma (62-64).

DISCLOSURES

The authors state no conflicts of interest.

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