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Pharmacogenetics of ophthalmic topical β-blockers

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Abstract

Glaucoma is the second leading cause of blindness worldwide. The primary glaucoma risk factor is elevated intraocular pressure. Topical β-blockers are affordable and widely used to lower intraocular pressure. Genetic variability has been postulated to contribute to interpersonal differences in efficacy and safety of topical β-blockers. This review summarizes clinically significant polymorphisms that have been identified in the β-adrenergic receptors (*ADRB1*, *ADRB2* and *ADRB3*). The implications of polymorphisms in *CYP2D6* are also discussed. Although the candidate-gene approach has facilitated significant progress in our understanding of the genetic basis of glaucoma treatment response, most drug responses involve a large number of genes, each containing multiple polymorphisms. Genome-wide association studies may yield a more comprehensive set of polymorphisms associated with glaucoma outcomes. An understanding of the genetic mechanisms associated with variability in individual responses to topical β-blockers may advance individualized treatment at a lower cost.

Keywords

β-adrenergic receptor; β-blocker; *CYP2D6*; glaucoma; IOP; polymorphisms; timolol

Glaucoma

Glaucoma is a group of heterogeneous ocular diseases defined by a progressive loss of the retinal ganglion cells, excavation or cupping of the optic nerve head, visual-field defects and, ultimately, blindness. With 70 million people affected with various forms of glaucoma, it is the second leading cause of blindness worldwide [1]. The primary risk factors include elevated intraocular pressure (IOP), aging, race and family history. In the general US population, it has been estimated that glaucoma affects 1–1.5% of people aged over 40–65 years, and 2–7% of those aged over 65 years. Prevalence varies with ethnicity; for example, the percentage of African–Americans affected with glaucoma ranges from 1.5 to 3.6% for those aged 40–65 years, and from 4.6 to 9.8% in individuals aged over 65 years [2].

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Although glaucoma is defined as a progressive optic neuropathy, it is associated with functional and structural impairments of the trabecular meshwork, optic nerve head and retinal ganglion cells (Figures 1 & 2). The ciliary body, positioned behind the iris, secretes aqueous humor that flows into the anterior chamber (Figure 2). The role of the aqueous humor is to nourish the avascular ocular tissues of the anterior segment: the posterior cornea, the trabecular meshwork and the lens. In addition, the aqueous humor collects metabolic biproducts and drains out into the trabecular meshwork at the periphery of the anterior chamber, called the anterior chamber angle (Figure 2). In total, 10% of the aqueous humor outflows from the anterior chamber through the ciliary body via uveoscleral outflow. The IOP is a measurement of the aqueous humor pressure inside the eye and ranges from 10 to 21 mmHg. Elevated IOP is the most common clinical risk factor associated with the onset and progression of glaucoma, and generally results from compromised drainage via the trabecular meshwork.

The broad clinical classifications of glaucoma are based on anatomical characteristics of the anterior chamber angle or the age of onset. Classifications as open-angle glaucoma and closed-angle glaucoma are based upon the status of the anterior chamber angle. Each category is then further divided into primary and secondary subtypes. Primary open-angle glaucoma (POAG) is the most common subset, representing over 70% of all cases of glaucoma [3], and is characterized by an open anterior chamber angle, elevated IOP and glaucomatous optic nerve changes. Although elevated IOP is a major risk factor for development of POAG, a great deal of investigation has recently focused on normal-tension glaucoma, where the progressive damage to the optic nerve occurs even with normal IOP [4]. In contrast to POAG, primary angle-closure glaucoma (PACG) refers to a condition where the anterior chamber angle is closed, resulting in elevated IOP and glaucomatous optic nerve changes; PACG is more common in Asian populations [5]. Primary congenital glaucoma is an inherited structural anomaly within the trabecular meshwork and the anterior chamber angle [6]. Secondary glaucoma is commonly associated with clinical syndromes such as Axenfeld–Rieger syndrome and Peters' anomaly [7]. Despite our ability to discriminate these glaucoma subtypes clinically, the pathophysiologic mechanisms underlying the onset and progression of most types of glaucoma remain unclear.

The molecular etiology of glaucoma, and the molecular mechanisms governing the disease's onset and progression, are vastly unknown. There is strong evidence that glaucoma has a genetic basis. To date, at least 14 candidate POAG loci have been identified [101]; however, causative alleles associated with glaucoma have been defined for only a few genes. Mutations in the myocilin gene were initially identified in families segregating juvenile-onset primary-angle glaucoma [8]. However, subsequent analysis of patients with POAG also identified myocilin mutations in approximately 3–5% of POAG patients [8-10]. Similarly, mutations in the optineurin [11] and *WDR36* genes [12] have also been demonstrated to lead to glaucoma, although the mechanism of action of these genes is not yet well understood. Mutations in *CYP1B1* have been associated with primary congenital glaucoma [6], whereas mutations in the *Pitx2*, *Foxc1* and *Pax6* genes have been identified in patients with Axenfeld–Rieger syndrome and Peters' anomaly [7]. Despite these observations, the genetic cause associated with glaucoma remains unknown in most clinical situations. A better understanding of the onset and progression of glaucoma is needed at the molecular level. Such an understanding would likely open the door to novel strategies for the management of this potentially debilitating disease.

Current glaucoma therapy

At present, there are no therapies available that prevent the development of glaucoma. Similarly, no therapies are available to reverse glaucoma-induced vision loss. However, a reduction of the IOP has been shown to protect against further damage to the optic nerve head

[13]. As such, early diagnosis and proper treatment allow most glaucoma patients to retain good visual function. Unfortunately, glaucoma is initially asymptomatic. There have been no studies to assess population screening for open-angle glaucoma as a means to prevent vision loss, and the US Preventive Services Task Force found insufficient evidence to recommend for or against routine glaucoma screening in primary-care practices [14]. Once diagnosed, drug efficacy is a pivotal concern, since treatment has the capability to slow and/or arrest the progression of the glaucoma-associated irreversible vision loss.

Current treatment of POAG, the most common form of glaucoma, as well as ocular hypertension, focuses on the reduction of IOP. Drugs are usually administered topically to lower IOP. If necessary, additional topical agents and/or systemic drugs can be added. Drug management of glaucoma commonly includes five classes of drugs: α-adrenergic agonists, β-adrenergic antagonists, cholinergic agonists, prostaglandin analogs and carbonic anhydrase inhibitors [5]. Table 1 summarizes the available glaucoma drug treatments. The two most commonly prescribed drug groups are prostaglandin analogs, such as latanoprost, and β-blockers, such as timolol maleate [15]. If drugs fail to reduce IOP, laser therapy (trabeculoplasty) is applied to the trabecular meshwork to increase aqueous outflow. In the event that the laser trabeculoplasty fails to control the IOP, surgical procedures are applied to create a new route for aqueous humor outflow [5].

In pediatric cases of primary or secondary congenital glaucoma, medical therapy often plays a supportive role to surgery [16]. In this context, topical β-blockers (first line) and topical carbonic anhydrase inhibitors (second line) are preferred [16]. Prostaglandin analogs have limited efficacy for lowering IOP in pediatric patients [17].

Efficacy & safety of β-blockers in glaucoma treatment

β-blockers are one of the most commonly prescribed groups of drugs in the USA [18]. They are prescribed for the treatment of a number of vascular (e.g., coronary artery disease) and non-vascular (e.g., glaucoma) diseases. In the treatment of glaucoma, when applied topically, nonselective β-blockers, such as timolol maleate, reduce IOP by 27–35% [19]. β-blockers reduce IOP by inhibition of aqueous humor production [20] and not by increasing aqueous humor outflow [21,22]. The population-based efficacy of timolol has been well documented in the treatment of glaucoma [19,23]. However, two recent studies reported that timolol was less effective in lowering IOP in black patients than in non-black patients [24,25]. Although the molecular mechanisms responsible for the lower efficacy of timolol in black patients remain unknown, it has recently been suggested that iris pigmentation and differential nonspecific binding of the drug may play a role [26]. Alternatively, polymorphisms in the drug target genes may be associated with variable clinical responses to timolol [26].

When β-blockers are topically administered, they can be absorbed through the conjunctival epithelium, lacrimal channels, nasal mucosa and GI tract into the systemic circulation [27]. As a result, topical β-blockers can induce systemic adverse drug reactions, including contraction of the bronchial smooth muscle, bronchospasm, respiratory failure and death. In addition, cardiac side effects include bradycardia, hypotension, decreased myocardial contractility, and heart failure [28-29]. Adverse ocular affects of topical β-blockers are minimal, but in some cases timolol was reported to cause hyperemia of the conjunctiva, burning, stinging or superficial punctate keratitis [30,31], and reduced tear flow [32].

Economic implications

Currently, in the USA, over 2 million people are affected with POAG. By 2010, that number is expected to grow to over 3 million [2]. In recent years, topical prostaglandins have become a common first-choice glaucoma therapy, partly owing to their relatively consistent clinical

efficacy, and partly owing to their lower frequency of adverse effects [19]. However, topical prostaglandin analogs are expensive, ranging from US$0.90 to US$1.25 per day [33]. The least expensive option for the medical therapy of glaucoma, generic timolol products, has been shown to cost between US$0.38 and US$0.50 per day [34]. In a study considering cost, efficacy and safety of ocular β-blockers, it was concluded that timolol maleate should be the formulary agent of choice because other agents have not shown an outstanding advantage for the cost difference [35]. Understanding the molecular mechanisms guiding variability in response to topical β-blockers will be critical for advancing a more personalized and less expensive approach to the treatment of glaucoma.

ADRB genes as pharmacodynamic candidates

The interindividual variability in IOP response to β-blockers is unclear. It has been well established that, for most therapeutics administered at standard doses, a substantial proportion of patients do not respond to drug treatment. While some patients respond only partially, others experience adverse drug reactions [36]. Genetic variability contributes a great deal to population-based differences in drug efficacy and safety [37]. The ADRB1, ADRB2 and ADRB3 adrenergic receptors are highly expressed in the eye [102], whereas ADRB1 and ADRB2 were specifically identified in the ciliary body, trabecular meshwork and optic nerve head [38]. Therefore, adrenergic receptors were proposed as pharmacodynamic candidate genes potentially associated with the interpersonal variability of IOP response to topical β-blockers.

Adrenergic receptors are members of the large superfamily of G-protein-coupled receptors. Epinephrine and norepinephrine are the primary endogenous agonists, but other endogenous catecholamines (e.g., dopamine) and a variety of exogenous ligands (e.g., isoproterenol) are also known to interact with these receptors. Historically, the adrenergic receptors have been subdivided into β1 and β2 subtypes, based upon their relative binding affinity for various catecholamines. In general, β1 adrenergic receptors demonstrate highest affinity for norepinephrine, intermediate affinity for epinephrine and lowest affinity for isoproterenol, whereas β2 adrenergic receptors demonstrate highest affinity for isoproterenol, intermediate affinity for epinephrine and lowest affinity for norepinephrine. Each subtype is then further subdivided according to known physiologic function (e.g., β1 receptors activate intracellular pathways with both chronotropic and inotropic cardiac effects).

Molecular biological techniques have revealed that there are at least three distinct β-adrenergic receptors, encoded by three separate genes (*ARDB1*, *ARDB2* and *ADRB3*) located at different chromosomal loci (chromosomes 10q25.3, 5q33.1 and 8p12, respectively). *ADRB1* and *ADRB2* are single-exon genes; the former is ultimately translated into a 477 amino acid protein, and the latter into a 413 amino acid protein. *ARDB3* has two exons and encodes a 408 amino acid protein. All three *ADRB* genes have a similar structure, comprising seven transmembrane domains, an extracellular amino terminus and an intracellular carboxy terminus [39]. *ADRB1* and *ADRB2* are expressed in the heart, and polymorphisms in both genes have been linked to hypertension and cardiovascular disease. In addition, genetic variations in *ADRB2* have also been linked to obesity and metabolic diseases. *ADRB3* is predominantly expressed in adipose tissue and is involved in lipolysis and thermogenesis.

All known *ADRB* genes contain functionally relevant polymorphisms. Sequence evaluation of *ADRB1* specifically identified two polymorphisms, Ser49Gly [40] and Arg389Gly [41]. *In vitro* functional analysis of *ADRB1* polymorphisms revealed that Ser49Gly is associated with the agonist-promoted downregulation of receptor expression and altered glycosylation [42]. The Arg389Gly *ADRB1* polymorphism, located within the intracellular domain near the

seventh transmembrane span, is in a region important for receptor G-protein coupling and the subsequent agonist-stimulated adenylyl cyclase activation [41].

Like *ADRB1*, the sequence evaluation of the *ADRB2* gene also identified two polymorphisms, Arg16Gly and Gln27Glu [43]. *In vitro* functional analyses of *ADRB2* polymorphisms have revealed that Arg16Gly is associated with the agonist-promoted downregulation of receptor expression, whereas the Gln27Glu polymorphism is resistant to receptor downregulation [43]. Both *ADRB1* and *ADRB2* polymorphisms have been associated with altered receptor function in a variety of clinical settings, including patients with congestive heart failure [44-45], nocturnal asthma [46], hypertension [47] and acute coronary syndromes [48].

Recently, a single polymorphism in the *ADRB3* gene has been associated with body composition in at least three separate populations [49-51]. In all three contexts, effect size was small and detection required adjustment for environmental covariates (e.g., gender and/or sedentary versus active lifestyle). This SNP, T727C, encodes an amino acid substitution (Trp64Arg) in the first transmembrane-spanning region of ADRB3, near its N-terminus. In a series of 695 adult Chinese subjects, this *ADRB3* SNP was associated with weight and BMI in men but not in women [52]. A similar effect was observed in 295 adult Japanese men, but only when the data were adjusted for energy intake [51]. In a study of 643 American women (representing both European and African heritage), no association was observed between this *ADRB3* SNP and any obesity phenotypes (i.e., BMI, waist circumference and waist:hip ratio [50]). The reason for gender discrepancy remains unclear and requires further characterization, since emerging data indicate that gender may impact phenotype in the context of glaucoma treatment [52].

The role of adrenergic receptor polymorphisms in variability of IOP response to β-blockers has recently been investigated. In healthy subjects, the Arg389Gly polymorphism in *ADRB1* has been associated with a higher baseline IOP and a greater reduction in IOP following topical betaxolol therapy [53]. Although the Ser49Gly polymorphism in *ADRB1* does not predict IOP response, it has been associated with higher systolic and diastolic blood pressure following treatment with topical timolol in healthy subjects and glaucoma patients [54].

Recent data indicate that *ADRB2* polymorphisms also influence clinical outcomes related to topical β-blockers. Our group evaluated the medical records of more than 18,000 adult subjects participating in a large population-based biobank [55-56]. Topical β-blockers had been prescribed for over 300 of these subjects, and over 200 of them had sufficient IOP data for the conduct of a pharmacogenetic association study. Males were significantly more likely than females to have a 20% or greater drop in IOP ($p < 0.01$). After adjusting for gender (and for family history of glaucoma), subjects with a homozygous major allele (CC) genotype at the Gln27Glu coding SNP in *ADBR2* were significantly more likely to experience a 20% or greater decrease in IOP (OR: 2.41; 95% CI: 1.00–5.82) [55]. It is noteworthy that ADRB2 is the predominant adrenoceptor subtype in the iris–ciliary body [38]. To date, polymorphisms in the *ADRB3* gene have not been associated with β-blocker variability in glaucoma therapeutic response or etiology of glaucoma.

Since ADRB2 is the predominant adrenoceptor in the iris–ciliary body, polymorphisms in *ADRB2* have also been hypothesized to play a role in the development of glaucoma as a disease process (i.e., in both the onset and rate of progression). In a Japanese cohort, POAG carriers of the Gly16 allele showed an earlier onset of the disease, and carriers of the Glu27 allele showed a higher IOP at the time of diagnosis [57]. However, these findings failed to replicate in a Turkish cohort [58], and in two ancestral US populations [59]. All clinically relevant polymorphisms identified in *ADRB* genes are summarized in Table 2.

CYP2D6 gene as a pharmacokinetic candidate

In general, many β-blockers are metabolized by a highly polymorphic drug-metabolizing enzyme, CYP2D6. The gene encoding the CYP2D6 enzyme is located on chromosome 22 q13.2; it contains eight coding exons, and it encodes a 446 amino acid protein. A total of 122 SNPs and/or short insertion/deletion polymorphisms have been reported within the *CYP2D6* genomic locus in human populations, resulting in at least 70 unique *CYP2D6* haplotypes [103].

Phase I oxidation by CYP2D6 inactivates many drugs within the β-blocker class. However, nearly 10% of the general population have a measurable deficit in their ability to metabolize CYP2D6 substrates. Patients with two functional copies of the *CYP2D6* gene (e.g., *CYP2D6*1/*1* homozygotes or *CYP2D6*1*/**2* heterozygotes) are often referred to as extensive metabolizers. Poor metabolizers have two copies of a null allele. Intermediate metabolizers have at least one copy of an allele with reduced enzymatic activity. Gene duplication also occurs (e.g., **2XN*), and these subjects are often referred to as having an ultrarapid metabolizer phenotype.

Clinically, ultrarapid metabolizers (e.g., *CYP2D6*2XN*) have been shown to have lower plasma concentrations of metoprolol than extensive metabolizers [60], and poor metabolizers (expression of several potential variant genotypic combinations introduced above) exhibit several-fold higher plasma concentrations of metoprolol than extensive metabolizers [61]. A decade ago, investigators showed that CYP2D6 poor metabolizers have higher circulating timolol levels and correspondingly lower heart rates following systemic absorption of topical timolol therapy [62]. Despite these observations, very few reports have directly addressed the impact of *CYP2D6* gene variants on the IOP-lowering efficacy of topical β-blockers.

Recently, it has been reported that CYP2D6 poor metabolizers demonstrate altered serum kinetics following administration of the aqueous formulation of timolol (0.5% aqueous timolol), but not for the hydrogel formulation (0.1% timolol hydrogel) [54]. These findings suggest that, in the absence of knowledge regarding a patient's *CYP2D6* genotype, it may be safer to prescribe the formulation (hydrogel) with the less variable kinetic profile. Further studies are needed to characterize the potential utility of prospective knowledge regarding *CYP2D6* genotype prior to initiating these drugs.

Conclusion & future perspective

It has been estimated that, worldwide, 60.5 million people will be affected with POAG and PACG by the year 2010, and this number will likely increase to 79.6 million people by the year 2020 [63]. The least expensive options for the medical therapy of glaucoma are topical β-blockers, such as timolol maleate. Results are emerging in support of *ADRB2* gene polymorphisms in predicting therapeutic response to topical β-blockers [56]. Future studies need to consider other polymorphisms in both pharmacodynamic and pharmacokinetic candidate genes, and the impact of variability in their gene products should be considered specifically within the context of their respective intracellular signaling pathways. Growing information regarding signal transduction networks activated by topical β-blockers (e.g., downstream effectors of *ADRB*), and expert knowledge regarding the absorption, distribution, metabolism and elimination of these drugs (e.g., biotransformation mechanisms beyond phase I oxidation by CYP2D6), will likely prove useful for informing the analysis of large datasets, as the pharmacogenetics community moves towards the scanning of whole genomes [64,65].

Executive summary

Glaucoma

- Glaucoma is the second leading cause of blindness worldwide.
- Elevated intraocular pressure (IOP) is the primary risk factor associated with glaucoma.

Current glaucoma therapy

- Topical β-blockers are widely used to lower IOP.

Efficacy & safety of β-blockers in glaucoma treatment

- Genetic variability contributes to population-based differences in drug efficacy and safety.

Economic implications

- Topical β-blockers are the least expensive option for treatment of glaucoma.

ADRB *genes as pharmacodynamic candidates*

- An *ADRB1* gene polymorphism has been associated with a higher baseline IOP and a greater reduction in IOP following topical betaxolol therapy.
- A recent study suggests that *ADRB2* gene polymorphisms may predict therapeutic response to topical β-blockers.

CYP2D6 *gene as a pharmacokinetic candidate*

- None of the *CYP2D6* polymorphisms have been found to be associated with interindividual variability in IOP response to β-blockers.

Conclusion & future perspective

- Additional genes and polymorphisms likely contribute to efficacy and safety of β-blockers in glaucoma treatment.
- Novel approaches, such as genome-wide association studies, will identify gene variants that are predictive of the individual drug efficacy and toxicity of β-blockers.
- Understanding the molecular mechanisms underlying variability in response to topical β-blockers will be critical for advancing a more personalized approach to glaucoma.

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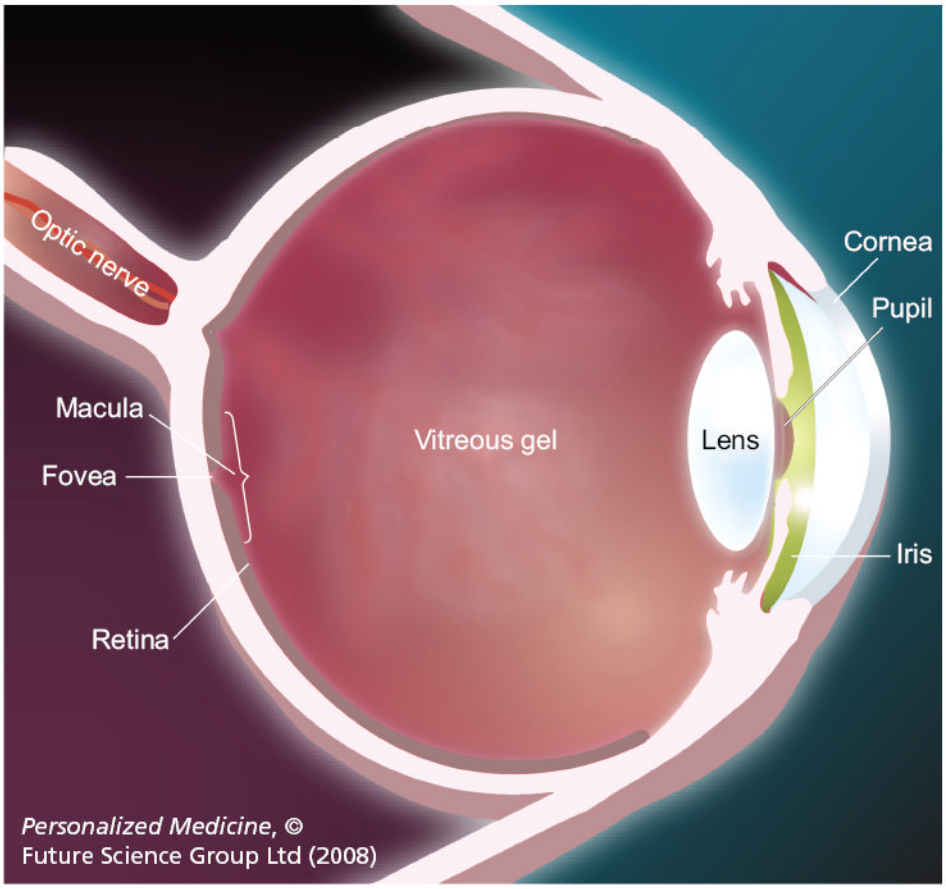
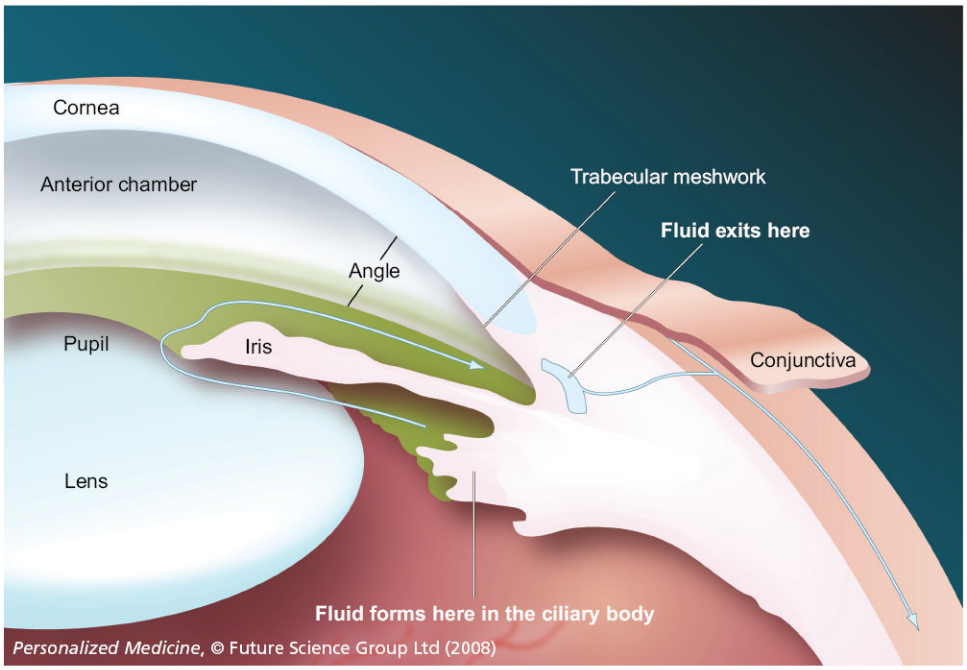


Modified from the National Eye Institute, NIH, USA.

Figure 1.
Human eye anatomy



The blue arrows depict aqueous humor secreted in the ciliary body outflowing through the pupil into the anterior chamber and draining into the bloodstream through the trabecular meshwork.
Modified from the National Eye Institute, NIH, USA.

Figure 2.
Anterior chamber Structures involved in aqueous humor production and outflow in the eye

Table 1

Current pharmacologic options for the treatment of glaucoma.

Drugs	Mechanism of action
β-adrenergic antagonists (β-blockers)	Decrease in aqueous humor production by blocking adrenergic β-receptors in the ciliary body
Prostaglandin analogs	Increase of aqueous humor uveoscleral outflow by decreasing the extracellular matrix in the ciliary body
α-adrenergic agonists	Both decrease of aqueous humor production and increase of aqueous humor outflow
Carbonic anhydrase inhibitors	Decrease of aqueous humor production by inhibition of carbonic anhydrase and decrease of bicarbonate production in the ciliary body
Cholinergic agonists	Increase of trabecular meshwork outflow by stimulating parasympathetic receptors at neuromuscular junctions

Table 2

Common functional polymorphisms due to coding SNPs in the *ADRB* genes.

Gene	Identified polymorphisms	Clinical relevance	Associated with interindividual variability in IOP response to β-blockers	Ref.
ADRB1	Ser49Gly	Yes	Yes	[53]
	Arg389Gly	Yes	No	[54]
ADRB2	Arg16Gly	Yes	No	[56]
	Gln27Glu	Yes	Yes	[56]
ADRB3	Trp64Arg	Yes	No	[51]

IOP: Intraocular pressure.