Glaucoma Pharmacogenetics

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Abstract

An individuals’ reaction to a specific drug is influenced by various factors including environmental, systemic and genetic factors. In most cases the reactions of a group of individuals are of the Gaussian type with non- to low responders at the lower end of the curve and high- to ultra-high responders at the upper end of the curve. As these extraordinary reactions to a drug are at least partly genetically determined pharmacogenetics is set to decipher the underlying genetic constitution and to establish an individualised genotype-based drug therapy. Candidate genes in pharmacogenetics include genes of receptors as well as their downstream pathway and genes of drug metabolising or activating enzymes. Most prominent examples from the medical literature are warfarin, clopidogrel and various psychotropic and oncological drugs. Regarding glaucoma therapy studies investigating the role of polymorphisms in the genes of β-adrenergic receptors, the important metabolising enzyme CYP2D6 and the prostaglandin F2α receptor have been performed. Results of these studies are presented and an outlook on the role of pharmacogenetics in glaucoma therapy will be provided.

Keywords

Glaucoma, pharmacogenetics, beta-blocker, prostaglandin analogues

The effect of a drug in terms of desired effects and undesired side-effects on an individual basis is still not 100 % predictable.1 Undoubtedly, this prediction would be a great advantage for patients’ safety and societies’ economies and therefore, it has been subject to research ever since drugs have been used in a scientific manner.2 In case of ultrarapid metabolisers (1–2 % of Caucasians) levels of a metabolised drug might be too low for the intended effect, whereas morphine levels after codeine medication might be dangerously high.4 Clopidogrel is a antiplatelet agent prodrug activated by CYP2C19, which activity – as is the case for CYP2D6 – depends on the genotype. Poor or intermediate metabolisers (2 % and 26 % in Caucasians, respectively) are therefore at increased risk for cardiovascular events or stent thrombosis compared to extensive or ultrarapid metabolisers.4 In case of ultrarapid metabolisers (1–2 % of Caucasians) levels of a metabolised drug might be too low for the intended effect, whereas morphine levels after codeine medication might be dangerously high.4 Clopidogrel is an antiplatelet agent prodrug activated by CYP2C19, which activity – as is the case for CYP2D6 – depends on the genotype. Poor or intermediate metabolisers (2 % and 26 % in Caucasians, respectively) are therefore at increased risk for cardiovascular events or stent thrombosis compared to extensive or ultrarapid metabolisers.4

Pharmacogenetics in Glaucoma

Lowering the intraocular pressure (IOP) is still the only effective therapy for glaucoma patients. However, responsiveness in terms of IOP lowering and toxicity varies greatly among patients. For ocular hypertensive drugs the term non- or low responsiveness is not universally defined and percentages of non- or low responders are infrequently provided. For example, low responsiveness for timolol and prostaglandin analogues has been commonly defined as IOP

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reduction below 15 % of the baseline IOP. Camras et al. reported rates of low responders of 18 % for latanoprost versus 28 % for timolol after three months, although 26 % of the latanoprost low responders converted to responders in the following visits up to six months, while conversion rate of the timolol low responders was only 6 %. After one month Choplin et al. found low responders for latanoprost in 38.2 % at all measurements (8 am, 12 pm, 4 pm) and for bimatoprost in 18.8 %, whereas rates for low responders at six months at all measurements were reported to be as high as 51.5 % for latanoprost and 29.3 % for bimatoprost, respectively. Rossetti et al. however found solely 4.1 % low responders for latanoprost after one month, while Aung et al. found low responders for latanoprost after one month between 10.3 % and 14.8 %. Even less is know regarding the other classes of hypotensive drugs. So although the exact rate is currently not known, there are obviously low responders, as ophthalmologists know from their daily practice. Furthermore, significant variability has also been reported regarding the cardiorespiratory effects of ophthalmic non-selective beta-blockers.

Target genes for pharmacogenetic studies in glaucoma therapy include receptors and their downstream pathway targets as well as metabolising or activating enzymes. To date, studies have been performed solely for the two main drug groups, i.e. beta-blockers and prostaglandin analogues.

Beta-blockers

The hypotensive effect of the beta-blockers is considered to be generated by decreasing aqueous humour production in the ciliary body via α-2-adrenoceptor and β2-adrenoceptor. The genes for these two receptors are ADRB1 (α1-adrenoceptor) and ADRB2 (β2-adrenoceptor). Metabolisation of the beta-blockers is, however, achieved basically via phase 1 oxidation through CYP2D6.

ADRB1 is a single exon gene located on chromosome 10q25.3, resulting in a 477 amino acid protein. Two polymorphisms with functional consequences have been described. Rs1801253 has been found at nucleotide 1165 resulting in a G to C substitution and consequently in an arginine to glycine substitution at codon 389 (G389R). The wild type allele has been associated with increased activity of the agonist-stimulated adenylyl cyclase and has been associated with systemic hypertension. Rs1801252 occurs at nucleotide 145 resulting in an A to G substitution and consequently at codon 49 in a serine to glycine substitution, and this common single nucleotide polymorphism (SNP) has been associated with agonist promoted downregulation of receptor expression. Investigating the association between these ADRB1 polymorphisms and clinical efficacy of betaxolol in 48 normal volunteers, Schwartz et al. reported a significantly increased IOP response in individuals with the rs1801253 wild type allele, while no association was found between rs1801252 and IOP response. This is in contrast to the results of a retrospective study including 215 glaucoma patients by McCarthy et al. who investigated the impact of polymorphisms of ADRB1, ADRB2 and CYP2D6 on the IOP response to topical beta-blockers. They reported no association between IOP response after topical timolol and rs1801252 and rs1801253 genotype. Using ophthalmic timolol, Niemeni et al. found higher diastolic as well as systolic blood pressure upon head-up tilt in individuals with the wild type allele of rs1801252. Like ADRβ1, ADRβ2 is a single exon gene resulting in a 413 amino acid protein, located on chromosome 8p12 with two functional common polymorphisms. Rs1042713 is a G to A substitution at nucleotide 147 resulting in an arginine to glycine substitution at codon 16 (G16R) associated with agonist downregulation of receptor regulation. The second one (rs1042714) is a G to C substitution at position 179 leading to the substitution of glutamic acid to glutamine (E27Q) and altered receptor function. McCarthy et al. found a significant association between an IOP decrease of 20 % or more in individuals with the CC genotype at rs1042714 (OR 2.0; CI 1.00–4.02). Interestingly, Fuchs-Jager-Mayr et al. reported no influence on IOP response of the two ADRB2 polymorphisms. In their study including 270 healthy individuals, IOP response was determined at 4 and 8 hours after the instillation of one drop of timolol. As mentioned above, CYP2D6 is one of the major metabolising enzymes in the human liver. Its respective gene is mapped to 22q13.2 and contains nine exons leading to a 461 amino acid protein. To date, more than 100 variants of CYP2D6 have been described. According to the enzymatic activity of the resulting protein these have been grouped as poor (≤14 % of Caucasians), intermediate, extensive and ultrarapid (2 % of Caucasians) metabolisers. Niemeni reported higher maximum plasma concentration after topical aqueous timolol in poor metabolisers, whereas plasma concentration after topical hydrogel timolol did not differ among CYP2D6 groups. They concluded that in contrast to extensive metabolisers, poor metabolisers might be more prone to systemic adverse effects. Investigating two polymorphisms of CYD2D6 (rs16947 and rs1135840), Yuan et al. found no association between these polymorphisms and IOP response in 123 glaucoma patients, but the CC genotype of rs16947 conferred reduced risk of timolol induced bradycardia. Likewise, McCarthy et al. reported that in their study the CYP2D6 functional group had no significant influence on IOP response.

Prostaglandin Analogues

Prostaglandin analogues are supposed to exert their hypotensive effect mainly via the prostaglandin F2α receptor (FP receptor). Therefore, genetic variants in the respective gene (PTGFR) might potentially explain the variability in IOP response to prostaglandin analogues. Sakurai et al. evaluated ten polymorphisms in PTGFR in 100 healthy volunteers after determining IOP response to latanoprost after seven days. Mean IOP reduction was found to be 18.1 % with 19 % low-responders, defined as IOP reduction below 10 % of baseline IOP. Two polymorphisms significantly correlated with mean IOP reduction. While the first is located in the promoter region (rs3753380), the second (rs3766355) lies in an intron one. A promoter assay revealed reduced transcriptional activity for the C allele of rs3766355 and the T allele of rs3753380. Additionally the authors investigated the impact of polymorphisms of proteins involved in the prostaglandin pathway (i.e. prostaglandin transporter, fatty acid amid hydrolase, FP receptor regulatory protein and matrix metalloproteinases), but found no significant correlation.

Discussion

Pharmacogenetics has the potential to guide patients and clinicians to a more personalised medicine. But up to now and despite numerous studies with positive results, only few pharmacogenetical tests have been incorporated in clinicians’ practice, which has been grossly attributed to educational and economic reasons.

Glaucoma therapy results from pharmacogenetical studies provided some evidence for the implication of different polymorphisms in IOP response and side effects. But limitations like missing replication studies, small sample size, and retrospective design of these studies are a major concern before introducing pharmacogenetical
tests in daily practice. Moreover, potential pharmacogenetical tests have to prove their utility regarding socioeconomic considerations. While direct-to-costumer personal genome testing companies like 23andme, deCODEme, Navigenics, Knome are constantly increasing their range of SNPs, also including pharmacogenetical target genes like ADRB1, the interpretation of such results regarding glaucoma therapy is still critical. To achieve robust results for correct interpretations, it seems to be necessary to perform large-scale prospective studies, including sufficient number of participants with excellent phenotyping regarding IOP response to glaucoma therapy. However, as prices for genotyping human DNA have been tremendously reduced in the last decade, it can be assumed that in the near future genetic data can be obtained at a reasonable price, yet most importantly, correct interpretations of these data through the results of pharmacogenetical studies have to be provided.