HHS Public Access

Author manuscript

Eur J Pharmacol. Author manuscript; available in PMC 2017 September 15.

Published in final edited form as:

Eur J Pharmacol. 2016 September 15; 787: 57–71. doi:10.1016/j.ejphar.2016.06.018.

Glucocorticoid Therapy and ocular hypertension

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Abstract

The projected number of people who will develop age-related macular degeneration in estimated at 2020 is 196 million and is expected to reach 288 million in 2040. Also, the number of people with Diabetic retinopathy will grow from 126.6 million in 2010 to 191.0 million by 2030. In addition, it is estimated that there are 2.3 million people suffering from uveitis worldwide. Because of the anti-inflammatory properties of glucocorticoids (GCs), they are often used topically and/or intravitreally to treat ocular inflammation conditions or edema associated with macular degeneration and diabetic retinopathy. Unfortunately, ocular GC therapy can lead to severe side effects. Serious and sometimes irreversible eye damage can occur as a result of the development of GC-induced ocular hypertension causing secondary open-angle glaucoma. According to the world health organization, glaucoma is the second leading cause of blindness in the world and it is estimated that 80 million will suffer from glaucoma by 2020. In the current review, mechanisms of GC-induced damage in ocular tissue, GC-resistance, and enhancing GC therapy will be discussed.

Keywords

glaucoma; glucocorticoids; steroid receptors; trabecular meshwork

1. Introduction

Glaucoma is a group of heterogeneous diseases resulting in optic nerve degeneration characterized by functional and structural impairment of ocular tissues (Dibas and Yorio 2004). Particularly affected are the trabecular meshwork (TM), the optic nerve head and retinal ganglion cells, the loss of the latter results in blindness. It is estimated that more than 2 million Americans have glaucoma and additional individuals have the disease but it is undiagnosed since there are no symptoms until peripheral vision deteriorates. Primary open angle glaucoma (POAG) is a late-onset disease with elevated IOP as the greatest risk factor associated with this disease. One to two percent of humans over 40 are diagnosed with POAG and the incidence among African American and Hispanic populations is especially high (Quigley and Brown 2006).

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Although a number of the risk factors have been identified (i.e., family history, elevated intraocular pressure (IOP), age, race, and sensitivity to glucocorticoids (GCs)), elevated IOP remains the key risk factor for the development and progression of primary open-angle glaucoma (POAG). Therefore, IOP lowering drugs have been the first line of defense in delaying the progression of the disease. The elevation of IOP in POAG results from increased aqueous humor outflow resistance and is associated with changes in TM cells accompanied by increased deposition of extracellular matrix material (ECM) (Tamm and Fuchshofer 2007; and Rönkkö et al., 2007) as well as differences in the ECM profile (see review by Vranka et al., 2015). GCs can induce similar changes in the TM ECM (Johnson and Gottanka 1997; and Zhou and Li 1998) that results in elevated IOP.

It is estimated that 1.2% of the US population is currently being treated with oral GCs (Overman et al., 2013). Two other studies estimated that glucocorticoids are still taken by around 2% of adults in the US at any given time (Ettinger et al., 2001; and van Staa et al., 2000).

Although anti-VEGF represent the first line of defense in the treatment of macular edema in macular degeneration and diabetic retinopathy, GCs, due to their powerful anti-inflammatory properties, are often used topically and/or intravitreally to treat ocular inflammation conditions or edema associated with macular degeneration and diabetic retinopathy (Haeck et al., 2011; and Noble and Goa 1998). More recently, GCs has been used in combination with anti-VEGF (Vakalis et al., 2015; Calvo et al.; and 2015, Lim et al. 2015) or photodynamic monotherapy (Selım et al., 2014). These combinations have been shown to have superior results than either treatment alone.

Over 2 million people worldwide are thought to have uveitis and in the United States uveitis with an incidence of 15 cases per 100,000 population (Foster and Vitale 2002) and 43,000 newly diagnosed cases a year (Vadot 1992). Women have a higher prevalence of uveitis than men, and the largest differences occur in older age groups (Gritz and Wong 2004). The use of steroid implants for noninfectious uveitis has been reviewed in Brady et al., 2016. Glucocorticoids are a mainstay of therapy of ocular inflammation and are either administered topically, regionally, or systemically. Regional application is done either by periocular injection or intravitreal injections. Periocular injections of GCs are effective in treating ocular inflammation (Sen et al., 2014). Approximately 20% of uveitis patients in the United States develop glaucoma that is not race, sex, or age-dependent. Glaucoma is much more common in chronic uveitis with incidence of 11% after 5 years. This differs from acute uveitis with, 7.6% of patients diagnosed with glaucoma after only 12 months (Herbert et al., 2004; and Neri et al., 2004).

Unfortunately, chronic use of GCs is associated with several deleterious side effects including: hepatic steatosis, osteoporosis, muscle wasting, growth retardation, infertility, cognitive dysfunction, glaucoma, cataracts, and topical skin thinning (Patel et al., 2014). In addition to humans, GCs have been shown to induce IOP elevation in rabbits (Lorenzetti 1970), cats (Zhan et al., 1992), dogs (Gelatt and Mackay 1998), cows (Gerometta et al., 2004), sheep (Gerometta et al., 2009), monkeys (Fingert et al., 2001), rats (Sawaguchi et al., 2005), and mouse (Whitlock et al., 2010).

The current review covers mechanisms controlling endogenous glucocorticoids regulation as well as steroid-induced changes in cells mediated by different glucocorticoid receptors. The review will also describe the cellular signaling mediating steroid-induced ocular hypertension and the damage inflicted on the trabecular meshwork with steroid use. In addition, we report on mechanisms of steroid-resistance in patients in order to help predict not only steroid responsiveness but also possible ways to minimize side effects.

2. GC-induced IOP elevation and age-dependence

There are differences in steroid responsiveness among the population, where topical ocular administration of GCs elevates IOP in approximately 30%–40% of the general population (also known as “steroid-responders”). In contrast, nearly all of POAG patients are steroid responders (Paterson 1965; Davies 1968; Schwartz et al., 1973; Meredig and Pulhorn 1980; and Bartlett et al., 1993).

Steroid responsiveness is defined differently. An elevation of 5 mmHg following steroid therapy has been defined as a steroid responder (Yamamoto et al., 2008). Others considered an IOP above 21 mmHg (Herbert et al., 2004) or 24 mmHg (Heinz et al. 2009) following steroid treatment as a steroid responder. However, another group considered the combination of both an increase of 5 mmHg and IOP above 24 as a steroid responder (Levine et al 2002). In this context, we shall consider all these referenced IOP elevations as a characteristic of steroid responder.

Surprisingly, children are especially susceptible to an IOP increase secondary to steroids (Tripathi et al., 1992). Although older patients are at increased risk, children have been shown to be greater steroid-responders as compared with adults with >60% of children being steroid-responders (Lam et al., 2005; Kwok et al., 1997; and Ng et al., 2000). For example fluorometholone (FML), which is a hydrophilic synthetic fluorinated corticosteroid with minimal corneal penetration, has been shown to induce steroid-induced glaucoma in children (Stewart and Kimbrough 1979; and Akingbehin 1983). Current prescribed steroid are shown in Table 1 for comparison.

3. Mechanisms that control levels of GCs

3.1. Physiological Fluctuations in cortisol levels

Glucocorticoids are secreted in a diurnal rhythm where levels of cortisol are the highest in the morning (~51 nM at 8 AM), but gradually decrease during the day and reaching the lowest levels at night (~14 nM at 8 PM). Such oscillations in cortisol secretion are synchronized with individuals activity level (Charmandari et al., 2011). Interestingly, nocturnal rodents (e.g., mice and rats) exhibit an inverse rhythm of endogenous glucocorticoid profile to humans, where peak plasma levels of corticosterone (rodent version of glucocorticoid) are at night and lowest concentrations occur during the day. In addition, it has been shown that IOP fluctuates diurnally and may be linked fluctuations to in to cortisol levels, where the greatest IOP occurs during the early morning mirroring high levels of plasma cortisol levels (Smith 1966). Patients with POAG have elevated blood levels of cortisol compared to age-matched subjects (Ray and Mehra 1977; Meredig and Pulhorn

1980; Rozsival et al., 1981; Schwartz and McCarty 1987; and McCarty and Schwartz 1991). Aqueous humor cortisol levels are also higher than plasma levels in both cataract and glaucoma patients (Rozsival et al., 1981).

3.2. Mechanisms controlling concentrations of cortisol extracellularly and intracellularly

A key mechanism involved in GC-induced actions occurs via feedback inhibition. Stress induces the release of corticotropin-releasing hormone (CRH) from the hypothalamus which stimulates the release of adrenocorticotropic hormone (ACTH) and cortisol from the pituitary and adrenal cortex, respectively. Cortisol acts via feedback inhibition of its own secretion by attenuating CRH and ACTH release (Sharma et al., 2013).

The plasma half-life of glucocorticoids ranges between 80 mins for cortisol and 270 min for dexamethasone, where min approximately 90% of endogenous circulating cortisol is bound with high affinity to the plasma protein corticosteroid-binding globulin (Schäcke et al., 2002), and the remaining 6% binds to albumin and 4% exists as free and active (Siiteri et al., 1982; and Meulenberg and Hofman 1990). Corticosteroid-binding globulin (CBG), or transcortin, is a 50–60 kDa high affinity plasma transport glycoprotein that binds cortisol in humans and corticosterone in rodents (Westphal 1986; and Hammond 1990). CBG also binds progesterone with relatively high affinity (Westphal 1986). However, many synthetic steroids, with the exception of prednisolone, have low affinity for the corticosteroid-binding globulin. Interestingly, while dexamethasone failed to bind mammalian CBG, it binds chicken CBG with equal affinity to corticosterone (Gould and Seigel 1978). CBG is secreted principally from hepatocytes with circulating concentrations ranging from 30–52 pg/ml (Torpy and Ho 2007). CBG is a substrate for neutrophil elastin enriched at sites of inflammation where it is cleaved releasing cortisol (Hammond et al., 1991). CBG's affinity for cortisol is diminished by elevated temperature (typically seen in fever and inflamed sites) such changes in temperature results in the release of cortisol (Cameron et al., 2010; and Lin et al., 2010).

While CBG-unbound cortisol passively diffuses across the plasma membrane, its intracellular bioavailability within the cell is controlled by two enzymes functioning in an opposing manner. 11β-Hydroxysteroid dehydrogenase type 2 (11β-HSD2) oxidizes cortisol into the inactive metabolite cortisone. In contrast, 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1, 292 amino acids) converts cortisone to cortisol (Gathercole et al., 2013). The biological activity of any glucocorticoid appears to depend on the presence of a hydroxyl group at position C11 of the steroid structure, and the inactivation of this group to a C-11 oxo group inactivates the steroid (Cope and Black 1958). Such a mechanism is crucial for the kidney where cortisol is known to activate mineralocorticoid receptor and its inactivation by 11β-HSD2 is of great importance. Polymorphisms (Cys468Ala and Gly534Ala) in the gene that encodes 11βHSD2 were found associated with hypertension (Melander et al., 2000). Such a regulation of GCs can be named as the "pre-receptor" mechanism, i.e., prior to activation of the glucocorticoid GRα receptor and its translocation to the nucleus for either activation of repression of genes. 11β-HSD isozyme expression has recently been described in the human and rodent eye (Stokes et al., 2000, Rauz et al., 2001; and Suzuki et

al., 2001), especially 11β-HSD1 in ciliary epithelial cells, suggesting a role in aqueous humor production and the regulation of intraocular pressure.

In the aqueous humor, the cortisol concentration is 14-fold higher than cortisone, suggesting a predominantly 11β-HSD1 reductase activity (Rauz et al., 2001). 11β-HSD2 appears to be restricted to the corneal endothelium. Carbenoxolone (CBX), an 11β-HSD1 and 2 inhibitor, decreased IOP significantly (Rauz et al., 2001). Although the study may suggest that the use of topical 11β-HSD1 inhibitors may be a novel therapeutic for glaucoma, CBX is a non-selective drug that blocks gap junctions and GABA receptors (Connors 2012). Nevertheless, while Anderson et al. 2009 have shown that three different 11β-HSD1 selective blockers (PF-904955, PF-3319913, and PF-3859622) completely blocked cortisone conversion in rabbits and inhibited pLuc-GRE luciferase activity, the group did not show any IOP changes in rabbit following their topical application (Anderson et al., 2009). Assays of cortisol-metabolizing enzymes in homogenates of human trabecular meshwork cells also indicated a marked increase in delta 4-reductase and the decrease in 3-oxidoreductase (Weinstein et al., 1985), indicating a possible imbalance in the endogenous cortisol pathways.

Studies on steroid metabolites led to the discovery of the IOP lowering cortisenes, including anecortave acetate. Anecortave acetate (AA) lowered IOP of glaucoma patients (5 of 6 patients showed significant reduction in IOP (Robin et al., 2008). Cortisenes lack GC activity and antagonistic effects due to the lack of 11β-hydroxyl group and oxidation of the C9–C11 carbons to form a double bond preventing rehydroxylation of the C11 position (lack of anti-inflammatory effects and GRα nuclear translocation (Clark 2007). Although the exact IOP lowering mechanism of action for anecortave acetate is currently not known, binding studies have identified phosphodiesterase 6-delta (PDE6D) as the target of anecortave. Overexpression of PDE6D in mouse eyes caused elevated IOP, and this elevation was reversed by topical ocular application of either AA or anecortave desacetate (AdesA) (Shepard et al., 2013).

3.3. Glaucoma is an age disease and glucocorticoid levels increase with aging

Van Cauter et al., have reported increases in plasma cortisol levels up to 50% between 20 and 80 years of age in both male and female subjects (Van Cauter et al., 1996). Growth hormone which inhibits 11β-HSD1 declines with aging (Iranmanesh et al., 1991; and Landin-Wilkelmsen et al., 1994). Whereas, circulating inflammatory cytokines IL-6 and TNF-α increase with age and they are known to stimulate 11β-HSD1 (Payette et al., 2003). Not surprisingly, both cytokines are elevated in POAG donor retinas (Gramlich et al., 2013; and Yang et al., 2011). However, while aqueous humor IL-6 levels were lower in POAG patients (Takai et al., 2012), TNF-α levels were higher (Sawada et al., 2010). In another study both cytokines were found to have increased in plasma of glaucomatous patients (Huang et al., 2010). Interestingly, increased systemic circulating 11β- HSD1mRNA is observed in blood with increasing age (Al Bakir et al., 2008). Hypertensive patients however, were reported to have reduced 11β- HSD2 activities (Henschkowski et al., 2008). Transgenic mice overexpressing TNF-α have both decreased mRNA levels and activity of 11beta-HSD2 in kidney tissue (Kostadinova et al., 2005), which may explain elevated cortisol levels. Overall, the above studies may explain in part prevalence of glaucoma in the

aged population and the link to elevated cortisol levels, however they do not explain why only ~ 30% of the population develops steroid-induced glaucoma. In contrast, 60% of children receiving steroids end up suffering from elevated IOP and glaucomatous onset. The exact mechanisms to explain such differences are still not clear but may involve epigenetics. Growing evidence suggests that epigenetics such as DNA methylation, histone modification, and microRNA induce changes in gene function without changes in nucleotide sequence. Epigenetic mechanisms therefore can switch the genome into active and inactive domains based on endogenous and exogenous environmental changes and developmental stages, which may help explain steroid inter-individual and population variability. For example, an increase in GRα methylation was associated with distressed children (Tyrka et al., 2012). Furthermore, De Rooij et al., 2012 reported decreases in GRα promoter methylation correlated with reduced stress levels in the human adult population (de Rooij et al., 2012). However, the same hypermethylation mechanism has also been shown to augment GC effects. For example, increased methylation of 11β-HSD2 was detected in rats prenatally exposed to stress (Jensen Peña et al., 2012) and patients who developed hypertension following prednisone treatment had hypermethylated 11β-HSD2 promoter (Friso et al., 2008). Also, diet can affect GRα methylation as high intake of folic acid during pregnancy enhanced methylation of GRα in rats (Burdge et al., 2009). It is speculated that epigenetic changes induced by factors such diet, stress, and environment, which may be initiated early during fetal development, can appear during early childhood or adulthood producing long-lasting effects (Newnham 2001). The only encouraging factor is that such epigenetic alterations can be reversible (Tyrka et al., 2012).

3.4. Role of Intracranial pressure in glaucoma development and link to cortisol levels

Intracranial hypertension has also been linked to elevated cortisol levels. Obese patients with reduced 11β-HSD1 activities have the biggest drop in intracranial hypertension (Sinclair et al., 2010). In contrast, brain injured patients with elevated intracranial pressure had elevated cortisol concentrations (Feibel et al., 1983). Interestingly, IOP-elevated patients have higher intracranial pressure (Wostyn et al., 2015). While higher intracranial pressure was reported to be protective in glaucoma subjects and animal models of glaucoma (Zhao et al., 2015; and Zhang et al., 2015), Nusbaum et al., 2015 have shown detrimental effects of intracranial pressure elevation on survival of mice retinal ganglion cells. Although Rauz et al., 2003 have shown that carbenoxolone, a nonspecific inhibitor of 11β-HSD1 and 2, lowered IOP in glaucoma patients, the authors did not investigate its effects on intracranial pressure. Also, the effect of selective 11b-HSD1 on intracranial pressure has not been investigated (Anderson et al., 2009).

3.5. Mechanism of GC activity

3.5.1. GRα—The clinical and cellular actions of GCs are mediated via a 95 kDa cytosolic α–isoform of the glucocorticoid receptor (GRα), a member of the nuclear receptor family of ligand-dependent transcription factors. Upon GC binding, GRα undergoes conformational change that exposes a nuclear import signal and translocates to the nucleus. The translocation mechanism is ATP-dependent and heat shock protein 90-dependent (as it is inhibited by geldanamycin) (Dibas et al., 2012).

Multiple translational sites can generate up to 8 different subtypes of GRα (i.e. GRα-A, GRα-B, GRα-C1, GRα-C2, GRα-C3, GRα-D1, GRα-D2, and GRα-D3, Oakley and Cidlowski 2011; and Chrousos and Kino 2005). Although the GRα-A and GRα-B isoforms are the most abundant GRα proteins in many cell-types, trabecular meshwork cells from the human eye preferentially express the GRα-C and GRα-D isoforms (Nehme et al., 2009). Unfortunately there are no published studies on the expression of the different GR subtypes in normal vs. glaucomatous TM tissues nor studies of such subtypes in steroid-responders vs. non-responders TM tissues. Such studies are essential in improving steroid ocular therapy and worth immediate attention. In addition, immature dendritic cells predominantly express the GRα-D isoforms, whereas mature dendritic cells predominantly express the GRα-A subtype (Cao et al., 2013). In rodents, GRα-C isoforms are highest in pancreas and colon and the GRα-D subtypes are highest in spleen and lung (Lu and Cidlowski 2005). Individual GR isoforms were stably transfected into Jurkat cells. Cells were treated with DEX for 48 h and it was found that the treatment induced apoptosis in ~ 30% of the cells expressing the GRα, -A, or -B isoforms and in 50% of the cells expressing the GR-C3 isoform (Wu et al., 2013). Therefore, the GRα-C isoforms have been suggested to be the most biologically active, while the GRα-D isoforms are the most deficient in glucocorticoid-mediated functions (Wu et al., 2013).

The GRα-D isoform is constitutively present in the nucleus and bound to certain GRE-containing target genes (Oakley and Cidlowski 2011). The GRα-D receptors are basic proteins. While the isoelectric point (IP) for GRαA–C ranges between 5.88 and 6.32, the IP for GRαa-D1-3 is 8.66–8.74 (unpublished observations, Dibas et al). The GRα-D isoforms are basic and could explain their nuclear presence even in the absence of GCs.

3.5.2. Post-translational modification of GRα—Typically, GRα basal phosphorylation is low, however, following addition of an agonist, GRα becomes hyperphosphorylated. The phosphorylation of the S211 residue is important in the transactivation mechanism of GRα (Blind and Garabedian 2008; and Chen et al., 2008). Other phosphorylation sites also appear important (Galliher-Beckley et al., 2011; and Avenant et al., 2010). In contrast, CpdA (a GRα modulator) does not cause an increase in S211 and S226 phosphorylation (De Bosscher et al., 2005; and Avenant et al., 2010). Furthermore, GCs can induce downregulation of the GRα via proteasomal degradation following K419 ubiquitination (Deroo et al., 2002). Interestingly, a triple GRα mutant with 3 Ser phosphorylation sites mutated to Ala (S212, S220, S234), failed to undergo proteasomal degradation, suggesting that hyperphosphorylation drives the onset of the ubiquitination-mediated proteasomal degradation of GRα.

The GRα is also a substrate for sumoylation, in which SUMO (small ubiquitin-related modifier) peptides are covalently attached to the receptor at specific lysine residues (Lys-277, Lys-293, and Lys-703). Sumoylation of GRα dramatically promotes its degradation and inhibits the transcriptional activity of the receptor in a promoter-dependent fashion through the recruitment of corepressors (Davies et al., 2008; Holmstrom et al., 2003, 2008; Le Drean et al., 2002; and Lin et al., 2006). Overexpression of SUMO-1 destabilizes the GRα and this can be prevented with a proteasome inhibitor (Le Drean et al., 2002). In HEK293 cells expressing wild-type GRα (wtGRα) or a sumoylation-defective GRα

(GRα3KR), the gene expression profiles revealed that dexamethasone regulated genes are affected by the GRα sumoylation (Paakinaho et al., 2014). Furthermore, recent reports have demonstrated that GRα is acetylated at Lys-494 and Lys-495 in response to glucocorticoids, and this modification impairs its antagonism of NF-κB (Ito et al., 2006; Nader et al., 2009; Charmandari et al., 2011; and Oakley and Cidlowski 2013). The same study reported that deacetylation of the GRα by HDAC2 was necessary for binding of the receptor to NF-κB and repression of downstream target genes. Knockdown of HDAC2 correlated with decreased sensitivity to corticosteroid treatment in primary alveolar macrophages, whereas overexpression of HDAC2 in alveolar macrophages from chronic obstructive pulmonary disease (COPD) patients exhibiting glucocorticoid resistance, restored their sensitivity to glucocorticoid therapy (Kassel and Herrlich 2007). In summary, posttranslational modification of GRα may play an important role in GC-resistance.

3.5.3 GRβ—The GR gene NR3C1 consists of 9 exons where exon-2 is the starting translating exon. However, the pre-mRNA has 2 exons at its end known as 9α and 9β, separated by an intron. Alternative splicing can generate either GRα or GRβ. The GRα contains 777 amino acids whereas the GRβ contains 742 amino acids (Oakley et al., 1996). The human GRβ shares with GRα the first 727 amino acids but has a unique 15-amino acid carboxyl terminus (Goecke and Guerrero 2006). However, in other species such as zebrafish and mice, alternative splicing occurs at exon 7 and intron 8, respectively (Schaaf et al., 2008; and Hinds et al., 2010). A similar intron inclusion also was reported in rat GRβ (DuBois et al., 2013). Alternative splicing is carried by a unique complex known as the spliceosome. The spliceosome has many components including serine-arginine (SR) proteins (SRps, Will and Luhrmann R 2011). Whereas the overexpression of SRP20 increased GRα levels, overexpression of SRP30c and SRP40 increased GRβ levels (Jain et al., 2012). The human GRβ also has 8 different subtypes due to alternative translational sites (termed; GRβ-A, GRβ-B, GRβ-C1, GRβ-C2, GRβ-C3, GRβ-D1, GRβ-D2, and GRβ-D3) (Oakley et al., 1996). This means that there may be 256 different combinations of GRα/GRβ hetero-dimer receptors depending on different subtypes expressed. This alternative splicing of the GRβ receptor eliminates the GC binding domain. GRβ has been shown to act as a dominant negative regulator of GC-induced activation of GRα-mediated gene regulation (Goecke and Guerrero 2006; and Lewis-Tuffin and Cidlowski 2006). Lewis-Tuffin et al., 2007 reported that RU 486 bound GRβ weakly and slowly induced its nuclear translocation. However, Kino et al., 2009 failed to observe any RU486-induced GRβ nuclear translocation. Three groups have recently shown that overexpression of GRβ affected mRNA expression positively and negatively in a gene-specific fashion, suggesting that that GRβ has its own intrinsic transcriptional activities independent of GRα (Kino et al., 2009; Lewis-Tuffin et al.; 2007, and Nagy et al., 2016). Nevertheless, this could be due to dimerization with other receptors or transcription factors. Whereas FKBP51 is involved in GC-independent transport of both GRα and GRβ from cytoplasm to nucleus, FKBP52 is only involved in nuclear transport of the GC-bound activated GRα (Zhang et al., 2008).

3.5.4 Other GR isoforms—At least three other unique GRα isoforms exist; GRγ, GR-A, and GR-P. GRγ is produced from splicing of the GR primary transcript from the intron separating exons 3 and 4, resulting in the insertion of a single arginine between the DNA-

binding zinc fingers of the DBD (Rivers et al., 1999; and Ray et al., 1996). GRγ exhibited half of the activity of GRα for target genes. However, a recent study revealed that GRγ binds degenerate glucocorticoid response elements (GREs) in genes that are not targets of GRα and therefore expands the genes susceptible to regulation by glucocorticoids (Thomas-Chollier et al., 2013). GR-A transcripts lack exons 5–7, which encode the amino-terminal half of the LBD, as a result of mRNA splicing from exon 4 to 8 has no known biological functions (Moalli et al., 1993). Failed splicing at the exon 7/8 boundary produces GR-P that lacks the carboxy-terminal half of the LBD (Moalli et al., 1993). The expression of GRγ, GR-A, and GR-P receptor has yet to be analyzed in normal vs. glaucomatous TM tissues and whether their levels vary in steroid-responders vs. non-responders TM tissues. Such studies could provide useful information in enhancing steroid ocular therapy.

4 Role of importins and exportins in GRα nuclear trafficking

The subcellular location of GRα is controlled by both the import and export of the receptor through the nuclear pore complexes. Import of GRα via importinα/β-based mechanisms is controlled via the nuclear localization (NL1) and (NL2) domains (Picard and Yamamoto 1987). Hakim et al have shown importin-7 siRNA attenuated fluticasone propionate-induced GRα nuclear translocation in U937 cells, a human macrophage cell-line (Hakim et al., 2013). Deletion studies showed that NL1 supports rapid and hormone-independent translocation of GRα, whereas NL2 facilitates slower and hormone-dependent nuclear import (Savory et al., 1999; Tao et al., 2006; and Echeverria et al., 2009). Interestingly, importin alpha selectively bound NL1 and both importin 7 and the importin alpha-importin beta heterodimer could import a GRα NL1 fragment (Freedman and Yamamoto 2004). In addition, importin 7, importin 8, and importin alpha bind GRα even in the absence of hormone (Freedman and Yamamoto 2004). Tanaka et al., 2003 have shown that fluorescently-tagged GRα translocated to the nucleus along with fluorescently-tagged importin-α but not fluorescently-tagged importin β (Tanaka et al., 2003). While there was evidence for GRα-GFP interacting with GFP-importin-α, no such binding was observed between GFP-GRα and GFP-importin-β (Tanaka et al., 2003).

Echeverria et al., 2009 found that importin β and the integral nuclear pore glycoprotein Nup62 interact with hsp90-GRa complex (Echeverria et al., 2009). Tao et al., 2006 have shown that importin-13 siRNA inhibited steroid-induced GRα nuclear translocation in A549 cells (Tao et al., 2006). GRα export appears to be more complex. Pharmacological blockade of exportin1/CRM1-mediated export abrogates the translocation of GRα to the cytosol (Savory et al., 1999; and Beck et al., 2008). A nuclear export sequence (NES) was identified in the GRα LBD on the basis of sequence homology (Carrigan et al., 2007), but so far no experimental confirmation via mutation analysis has been performed. Carrigan et al 2007 identified a nuclear-retention signal (NRS) in GRα. This NRS, which overlaps closely with the NL1 in the hinge region of GRα, can actively counteract the redistribution of GRα to the cytoplasm after steroid withdrawal (Carrigan et al., 2007). In fact, following DEX removal only 50% of RFPGRα was exported back to cytosol 12hr post DEX withdrawal in transformed TM5 cells, a human trabecular meshwork cell-line (Dibas et al., 2012). Such persistent presence of GRα may therefore predict augmented gene regulation by steroids as the receptor is slow to be exported back to the cytosol. Such a mechanism may explain some

of the side effects of steroids including sustained IOP elevation. A proposed model for GR trafficking is shown in Fig. 1.

5. GC-induced regulation of gene expression

Following glucocorticoid binding, GRα induces or represses the transcription of target genes which can comprise up to 10–20% of the human genome (Galon et al., 2002). Surprisingly, glucocorticoid binding sequences are not located in the promoter region in close proximity to the transcription starting regions but are present in intragenic regions with > 11 kb from the transcription starting regions (Kuo et al., 2012) that either induce gene activation or repression. Reddy et al., have shown that while the GRE sequence of DEX-induced genes is located at a median of 11kb from the transcription start site, the nearest GR binding for genes repressed by DEX is at a distance of 146 kb from the transcription site (Reddy et al., 2009). Genes induced by DEX in TM include; serine protease inhibitor (alpha1-antichymotrypsin), pigment epithelium-derived factor (PEDF), cornea-derived transcript 6, prostaglandin D-2 synthase (Lo et al., 2003), secretory leukocyte protease inhibitor (SLP1), serum amyloid A2 (SAA2), Angiopoietin-Like 7 protein (ANGPTL7), serum amyloid A1 (SAA1), Serpin Peptidase Inhibitor, Clade A3 (SERPINA3), Zinc finger and BTB domain containing 16 protein (ZBTB16) (Rozsa et al., 2006), myocilin (MYOC) and Growth arrest-specific protein 1 (GAS1) (Fan et al., 2008). Known genes repressed by DEX include Sentrin-specific protease 1 (SENP1), Zinc finger protein 343 (ZNF343), and sex Determining Region Y)-Box 30 (SOX30) (Fan et al., 2008).

GC-induced GRα activation occurs via at least 3 different mechanisms (Beck et al., 2009; and Sundahl et al., 2015). GRα forms a dimer, binds to the glucocorticoid response element (GRE), and activates the promoter (Chalepakis et al., 1990). Another mechanism that has been suggested is that the GRα monomer binds to DNA with a transcription factor to cooperatively enhance gene expression (Morin et al., 2006). Alternatively, GRα can interact with transcription factors directly without interacting with DNA (also known as tethering, Johansson-Haque et al., 2008). GC-induced GRα-gene repression occurs via 4 potential mechanisms (Beck et al., 2009; and Sundahl et al., 2015). GRα can bind a transcription factor and thereby inhibit it from activation. This appears to be the predominant transrepression mechanism and is called tethering. A well-known example for such sequestration of factors is the inhibition of NF-kβ and activator protein 1 (AP-1) (De Bosscher et al., 2006; and Beck et al., 2009). A second repression method involves a transcription factor overlapping with the GRE where its subsequent binding to GRE blocks the transcription factor from binding (a form of competitive binding, Meyer et al., 1997). A third mechanism involves “Composite” GREs that consist of DNA binding sites (DBS) for GRα which, in association with binding sites for other factors, can act synergistically to mediate transrepression (Surjit et al., 2011). Finally, GRα binds to a negative GRE (nGRE), resulting in transcription repression (Stahn and Buttgereit 2008; and Beck et al., 2009).

GCs have been hypothesized to exert their anti-inflammatory effects due to transrepression via the GRα monomer formation, while GR-induced side effects are caused by transactivation due to dimerization of GRα. For example, while GC-induced hyperglycemia and muscle wasting are caused by transactivation, hypothalamic-pituitary adrenal axis

suppression is caused by transrepression (Patel et al., 2014). Osteoporosis is caused by both transactivation and transrepression (Schacke et al., 2002; and Carballo-Jane et al., 2004). In addition, GRα-induced transactivation is involved in anti-inflammatory factors such as annexin-1 (Parente and Solito 1994) and the leucine zipper (Cannarile et al., 2001).

The hypothesis that the GRα monomer mediates transrepression was postulated based on the GRα mutant harboring GRA458T mutation in the DBD (Heck et al., 1994; and Reichardt et al., 1998). This mutant cannot form dimers and has impaired GRα transactivation, yet it exhibited transrepression (Heck et al., 1994; and Reichardt et al., 1998). However, this simple explanation of transrepression vs. transactivation mechanisms can be easily challenged. First, GRα can still dimerize not only via the DBD, but also via an LBD (Bledsoe et al., 2002). Second, using immunoprecipitation and the “Number and Brightness” technology, the GRdim variants still showed GRα dimer formation in solution but significantly less than wild type (Jewell et al., 2012; and Presman et al., 2014). Nevertheless, GRdim mutant showed weakened GRE binding (Presman et al., 2014) and prednisolone-induced gene expression was greatly reduced compared to wild type (Frijters et al., 2010). The ability of prednisolone in GRdim mice to still induce genes raised speculation on the existence of alternate GRα dimers involving NTD-LBD contacts, GRα:MR heterodimers, or GRα multimeric complexes (Nixon et al., 2013). GRdim/dim mice still express normal mRNA levels of the GRα-dependent phenylethanolamine-*N*-methyltransferase (Adams et al., 2003). Therefore, the GRα’s ability to repress or activate genes is not simply dependent on its monomer or dimer status but rather the GRα-binding sequences and cofactors involved. There are no studies examining effects of steroids in the GRdim mice and whether fewer side effects would be anticipated. It would be very interesting to examine if DEX-induced IOP elevation would be attenuated in GRdim mice or not. That may indicate the involvement of non GRs in mediating side effect.

6. Mechanism of steroid-induced secondary ocular hypertension

Clinical trials have shown that GC-induced IOP elevation can occur within hours (Weinreb et al., 1985) or weeks when used topically (Armaly 1963), and years if used systemically (Bernstein et al., 1977). It appears that GC-induced IOP is both GRα-dependent and independent. For example, the rise in steroid-induced IOP is formulation dependent. For example, steroid acetates are lipophilic and tend to penetrate the cornea better than other derivatives such phosphates (hydrophilic) and not surprisingly, while dexamethasone acetate 0.1% produces ~ 22 mmHg rise, medrysone 1.0% caused a modest 1.0 mmHg rise in IOP (Jones and Rhee 2006). Also, sudden and acute increases of vitreous volume have been shown to induce a sharp increase in IOP. For example, injection of 0.1 ml of TA, 0.09 ml pegaptanib, and 0.05 ml bevacizumab produced increases IOP with the TA group having the highest IOP elevation followed by the pegaptanib and bevacizumab treated group (Bakri et al., 2003). In addition, fine white crystalline opacities following TA injection have been observed and such particulate material is suggested to occlude the trabecular meshwork (Singh et al., 2004). Therefore, some of the GRα-independent factors that can elevate IOP include formulation, intravitreal injection volume, particulate size and appearance. However, the previous effects tend to be short-term.

6.1. Mechanism of glucocorticoid (GC)-induced damage in trabecular meshwork

Similar to POAG, GC exposure increases aqueous humor (AH) outflow resistance. This is mediated in part by increased deposition of extracellular matrix (ECM) proteins due to inhibition of metalloproteases (MMPs) while increasing their natural blockers known as tissue inhibitors of metalloprotease (TIMP) (Li et al., 2011). GCs induce build-up of fine fibrillar-like material in the JCT and deposits of type IV collagen, heparin sulfate proteoglycan, and fibronectin (Tawara et al., 2008). Similar changes have been observed in human perfused donor eyes (Clark et al., 1995). DEX increases synthesis of unbreakable glycosaminoglycans (GAGs) (Johnson et al., 1990). Considerable amounts of GAGs in DEX-treated samples (48hrs) remained undigested after sequential treatment with hyaluronidase, chondroitinase AC, chondroitinase ABC, keratinase, and heparatinase (Johnson et al., 1990). DEX also increases β3 integrin via the Nuclear factor of activated T-cells 1c (NFAT1c) transcription factor (Faralli et al., 2013). DEX treatment induces a 2-fold and ~ 4-fold increase in HTM and rabbit TM cell stiffness and elevates the expression of matrix proteins (decorin, myocilin, and fibrillin, secreted frizzle-related protein (SFRP1) (Raghunathan et al., 2015), and increases protein levels of ZO-1 and Cx43 in both NTM and GTM cells (Zhuo et al., 2010). Tektas and Lutjen-Drecoll, 2009 have shown differences between POAG and steroid-induced glaucomatous TM tissues. Steroid-induced glaucomatous TM showed increased deposits of collagen type IV throughout the layers of the TM (Tektas and Lütjen-Drecoll 2009).

GC-induced trabecular meshwork dysfunction includes inhibition of phagocytosis (Zhang et al., 2007) and a major reorganization of the cytoskeletal cellular network and production of CLANS (Clark et al., 1994). CLANS are cytoskeletal tangles of actin filaments that influence stiffness and contractility of TM. Cdc42 is a Rho GTPase and an important modulator of the cytoskeleton and is induced by DEX (Qiu et al., 2015). However, its role in CLAN formation is not known. DEX also induces the upregulation of noncanonical Wnt ligand Wnt5a that can induce CLAN formation through the noncanonical Wnt receptor Tyrosine-protein kinase transmembrane receptor ROR2/Ras homolog gene family, including A/Rho-associated protein kinase 1 (ROR2/RhoA/ROCK) signaling axis (Yuan et al., 2013). DEX and transforming growth factor β 2 (TGFbeta2) significantly induce the upregulation of alkaline phosphatase (ALP) activity in trabecular meshwork primary cell lines. In glaucomatous human trabecular meshwork there is a significantly higher level of ALP activity than normal eyes (Xue et al., 2007).

6.2. Role of myocilin in GC-induced TM damage

MYOC is expressed in multiple ocular and nonocular tissues and despite intense investigation the function of this protein is largely unknown. It spans approximately 17 kb and contains 3 exons transcripting a 2.3 kb gene product. It contains 504 amino acids (Kubota et al., 1998; and Fingert et al., 1998) and has a predicted molecular weight of approximately 57 kDa. The MYOC protein has 2 major domains with a N-terminal myosinlike domain and a C-terminal olfactomedin-like domain. Although myocilin is expressed in many tissues, its abnormal or mutant isoforms has only been shown to ocular diseases. Mutation in the C-terminal of myocilin is linked to >10% of childhood glaucoma and ~ 3–5% of adult glaucoma (Stone et al., 1997; Wiggs et al., 1998; and Adam et al.,

1997). To date, 101 out of 266 mutations have been associated with glaucoma pathology (www.myocilin.com). Interestingly, while one mutation in exon-1 and 9 mutations in exon-2 were reported, the remaining 91 mutations occur in exon-3. Although GC-induced production of myocilin, when studying 70 human steroid responders and 114 control subjects no link between MYOC mutations and steroid-induced ocular hypertension has been detected (Fingert et al., 2001).

7. Mechanisms of GC-resistance

At least 10 different mechanisms have been discovered that explains GC-resistance. For example, polymorphisms of GRα gene has been implicated in GC-insensitivity therapy. First, the ER22/23EK polymorphism found in exon 2 was associated with decreased GRα transcriptional activity in reporter assays and decreased expression of endogenous genes compared to wild-type GRα (Russcher et al., 2005). Second, a mutation in the DNA-binding domain of the glucocorticoid receptor has been described in a patient with glucocorticoid resistance syndrome (Ruiz et al., 2001). The third mechanism that explains attenuated GC response has been proposed to be due to the elevated ratios of GRβ:GRα. GRβ acts as a dominant negative receptor and blocks steroid-induced gene expression. Overexpression of RFPGRβ inhibited DEX-induction of plasminogen activator inhibitor-1 (PA1) (Fig. 2). A higher ratio of GRβ to GRα appears to make TM cells more resistant to GCs (Zhang et al., 2005; Zhang et al., 2007; and Zhang et al., 2008). Interestingly, it has been shown that overexpression of SRP20 increases GRα levels and converts normal TM GC-resistant cells into CG-sensitive cells. In contrast, overexpression of SRP30c and SRP40 increases GRβ levels and converts GC-sensitive TM cells into GC-resistant ones (Jain et al., 2012).

Overexpression of hGRβ in Hela S3 cells can inhibit GC-induced reporter induction (Webster et al., 2001). Moreover, the viral transduction of mouse hybridoma GRβ-deficient cells with GRβ made the cell GC-resistant (Hauk, et al., 2002). While mRNA of hGRβ was detected in most tissues, hGRβ protein appears restricted and is only enriched in immune cells (T-lymphocytes, macrophages, peripheral blood mononuclear cells (PBMCs), and eosinophils, Oakley et al., 1996). In fact, in TM cells, the only way to detect hGRβ is by immunoprecipitation studies followed by western blot on immunoprecipitated fractions (unpublished observations, Dibas et al). The inability to detect hGRβ protein in many tissues and the lower expression mRNA levels compared to hGRα raised questions about the importance of hGRβ in tissues. However, numerous studies have shown that the difference in the ratio of GRβ:GRα is involved in the pathology of many diseases. Patient PBMCs and CD3+T GC-resistant cells had high GRβ levels (Hamid et al., 1999; and Leung et al., 1997). Similar findings were reported in lungs of fatal asthma subjects compared to normal (Christodoulopoulos et al., 2000). In addition, T cells and macrophages showed higher GRβ in GC-resistant asthma individuals (Sousa et al., 2000). PBMCs from GC-resistant ulcerative colitis showed higher hGRβ expression and no change in hGRα (Honda et al., 2000; and Orii et al., 2002). Finally, GC-resistant leukemia patients have higher GRβ:GRα ratio (Shahidi et al., 1999; and Longui et al., 2000). Elevated levels of GRβ also result from a naturally occurring polymorphism (A3669G) in the 3′-untranslated region of the GRβ mRNA that disrupts an mRNA destabilization motif (AUUUA) (Derijk et al., 2001).

However, two cytokines IL5 and IL13 which contribute to the asthmatic phenotype and suppressed by GRα are also GRβ repressed. GRβ mimicked GRα-induced suppression of IL5 and IL13 by recruiting HDAC1 to their promoters (Kelly et al., 2008). Another study has shown that the inhibition of HDAC using trichostatin-A in rodents exacerbated the inflammatory response in an LPS-induced myocarditis model (Zhang et al., 2012). Interestingly, Knockdown of HDAC2 correlated with decreased sensitivity to corticosteroid treatment in primary alveolar macrophages, and overexpression of HDAC2 in alveolar macrophages from COPD patients exhibiting glucocorticoid resistance restored their sensitivity to glucocorticoid therapy (Kassel and Herrlich 2007).

An additional mechanism of GC-resistance is caused by GRγ overexpression. GRγ expression in childhood acute lymphoblastic leukemia has been shown to correlate with resistance to dexamethasone treatment (Beger et al., 2003). Also, GR-P is linked to GC-resistance as it is the predominant splice variant in many glucocorticoid-resistant cancers (de Lange et al., 2001; and Krett et al., 1995). A mechanism in GC resistance in primates involves the FK-506 binding immunophilin FKBP51 (Reynolds 1999; and Scammell et al., 2001). Whereas FKBP51 is involved in GC-independent transport of both GRα and GRβ from cytoplasm to nucleus, FKBP52 is only involved in nuclear transport of the GC-bound activated GRα (Zhang et al., 2008). Not surprisingly, FKBP51 overexpression induced GC-resistance in human (Holownia et al., 2009) and animals (Westberry et al., 2006; and Scammell et al., 2001). It is likely that FKBP51 transports AP-1 and GRβ which both compete with GRα (Westberry et al., 2006; and Scammell et al., 2001).

GC-resistance may be induced by different factors that may be related to mutations in either the GR gene itself affecting its transcription or DNA binding. Other important regulations of resistance are mediated by competing GR receptors such as GRβ, GRγ, and GR-P, or transporting immunophilins (FKBP51). Stress also appears to be a dominant player in GC-resistance as is posttranslational modifications of GRα by phosphorylation, ubiquitination, acetylation, and sumoylation.

8. Prediction of glucocorticoid therapy outcome

Achieving successful GC therapy for uveitis, AMD, and diabetic retinopathy is dependent on steroid-responsiveness, GC-sensitivity, and reducing ocular side effects. Numerous attempts have been made to develop assays assessing glucocorticoid sensitivity in inflammatory disorders. Glucocorticoid sensitivity can be evaluated *in vivo* by assessment of the cortisol response during a low-dose oral or intravenous dexamethasone suppression test (DST) assuming that the dose will cause inhibition of ACTH secretion which in turn reduces cortisol levels. However, healthy populations have variable cortisol levels after a DST, which indicates individual differences in glucocorticoid sensitivity. It has been shown that serum cortisol levels were higher in the glaucomatous group compared to normal subjects. Systemic administration of cortisone reduced cortisol levels in the glaucomatous patients compared with the control group (Freedman et al., 1976). Although dexamethasone's half-life is almost four times that of cortisol (270 min vs. 80 min) and does not bind CBG protein as cortisol does, cortisol levels were not suppressed by orally administered dexamethasone in glaucoma patients (Schwartz and Levene 1972; and Rosenberg and Levene 1974).

However, measuring the negative feedback with the low-dose DST gives only an indication of glucocorticoid sensitivity in the pituitary gland and may not reflect what occurs in other tissues. Also, glucocorticoids can downregulate the expression of the glucocorticoid receptor in various cell types to compensate for glucocorticoid overexposure (Silva et al., 1994). In addition, Kass et al., 1976 and Klemetti 1990 followed 174 GC-responder patients and concluded that the plasma cortisol suppression testing may not actually predict the development of primary open-angle glaucoma in GG responders. However, POAG patients had a greater cutaneous vasoconstrictor response to glucocorticoids than patients with elevated IOP and normal subjects (Stokes et al., 2003). More work is needed in order to predict GC-responsiveness.

9. Selective glucocorticoid receptor agonists (SEGRAS)

Based on the questionable hypothesis that GC-induced anti-inflammatory effects are due to transrepression while side effects are due to gene transactivation, researchers have been looking for a selective dissociated GRα modulator where such an “ideal” drug induces transrepression (i.e., anti-inflammatory effects) without gene transactivation (i.e., side effects). Such dissociated compounds could be either selective glucocorticoid receptor agonists (SEGRAs) or modulators (SEGRMs) (Rosen and Miner 2005; and Beck et al., 2009). The first and most widely studied drug was (4-acetoxyphenyl)-2-chloro-N-methyl-ethylammonium chloride (compound A, CpdA) (De Bosscher et al., 2005). Unlike GCs, CpdA does not cause GRα dimerization nor did it allow binding of GRα to GREs and failed to induce GRα transactivation of reporter genes (De Bosscher et al., 2005; Dewint et al., 2008; Robertson et al., 2010; and 2013; and Presman et al., 2014). CpdA and another SERGA known as “ZK 216346” elicit partial or full nuclear translocation (De Bosscher et al., 2005; Dewint et al., 2008; Robertson et al., 2010 and 2013; Presman et al., 2014; and Drebert et al., 2015). In contrast, CpdA failed to induce RFPGRα nuclear translocation in TM5 cells (Dibas et al unpublished observations). In addition, CpdA functions as an AR antagonist (Zheng et al., 2015). CpdA promoted the interactions between GRα and NF-κB (Zheng et al., 2015) and attenuated nuclear factor (NF)-κB, indicating induction of GRα-mediated transrepression and the expression of NF-κB-related molecules. Matrix metalloproteinase-2, matrix metalloproteinase-9, interleukin-6, and vascular endothelial growth factor, were significantly down-regulated by CpdA. However, CpdA is unstable due to alkylating potential and its clinical usefulness is limited (Rauner et al., 2013). A new SEGRA termed “GW870086X” like DEX exhibits full trans-repressive activity, however, its transactivation is dramatically diminished compared to DEX (Uings et al., 2013). Nevertheless, GW870086X exerted potent anti-inflammatory effects in rodent models of both lung and delayed-type hypersensitivity induced inflammation (Uings et al., 2013). Similar to DEX, GW870086X increased myocilin secretion. However, GW870086X failed to increase fibronectin or decrease MMP2, effects exerted by DEX. Interestingly, while DEX decreased tissue plasminogen activator (tPA), GW870086X increased it (Stamer et al., 2013). Yet, there is no data on GW870086-induced IOP modulation.

Interestingly, another SERGA “BOL-303242-XC” moderately increased IOP in normotensive rabbits compared to dexamethasone and induced minimal induction of mRNA and protein myocilin compared to DEX or prednisolone in monkey TM cells (Budzynski et

al., 2009). A Phase III trial has been initiated to evaluate an ophthalmic suspension of BOL-303242-X for the treatment of inflammation following cataract surgery (sponsored by Bausch & Lomb). BOL-303242-X is also in clinical trials for the topical treatment of allergic conjunctivitis. However, the results of these clinical trials have not yet been disclosed and no SEGRA has yet been approved for clinical use.

10. Conclusion

Glucocorticoids are potent drugs with unsurpassed anti-inflammatory effects. However, glucocorticoid-based therapies are still a challenge for clinicians due the variability in glucocorticoid responsiveness among individuals and side effects. This is especially complicated as there are many factors that cause GC-resistance including altered expression of GRα isoforms. The expression of GRγ, GR-A, GR-P, and GRα subtype receptor have yet to be analyzed in normal vs. glaucomatous TM tissues and whether their levels vary in steroid-responders vs. non-responders TM tissues. Such studies are essential in improving steroid ocular therapy and worth immediate attention. It is also as important to follow whether epigenetic changes induced by environmental/diet can be inherited. As such epigenetic modifications are reversible, it would be interesting to utilize epigenetics in the prediction of GC-therapeutic outcome which may attenuate steroid-unwanted side effects.

Nevertheless, there are promising advancements. The ongoing clinical testing of SEGRAs or selective GRα dissociated ligands is underway which may help reduce adverse side effects commonly seen in patients receiving GC-therapy. Finally, based on clinical observations on IOP elevation in patients following intravitreal steroids (injections or implants), it has been recommended to follow IOP in patients immediately (30 min), at 1-week and 2-weeks, and monthly for up to 6 months following intravitreal injection of TA (Kiddee et al., 2013). The same report also recommended IOP measurement in patients receiving steroid implants at 2-weeks, 4-weeks, and monthly for up to 6 months following DEX implants and 9 months after fluocinolone implants. While glucocorticoids are a mainstay drug for inflammatory conditions, the side effect of increasing intraocular pressure remains a great risk to develop glaucoma. Understanding the mechanisms responsible for this action continues to remain an important area for study.

Acknowledgments

This work was supported by a grant from the National Eye Institute (EY016242).

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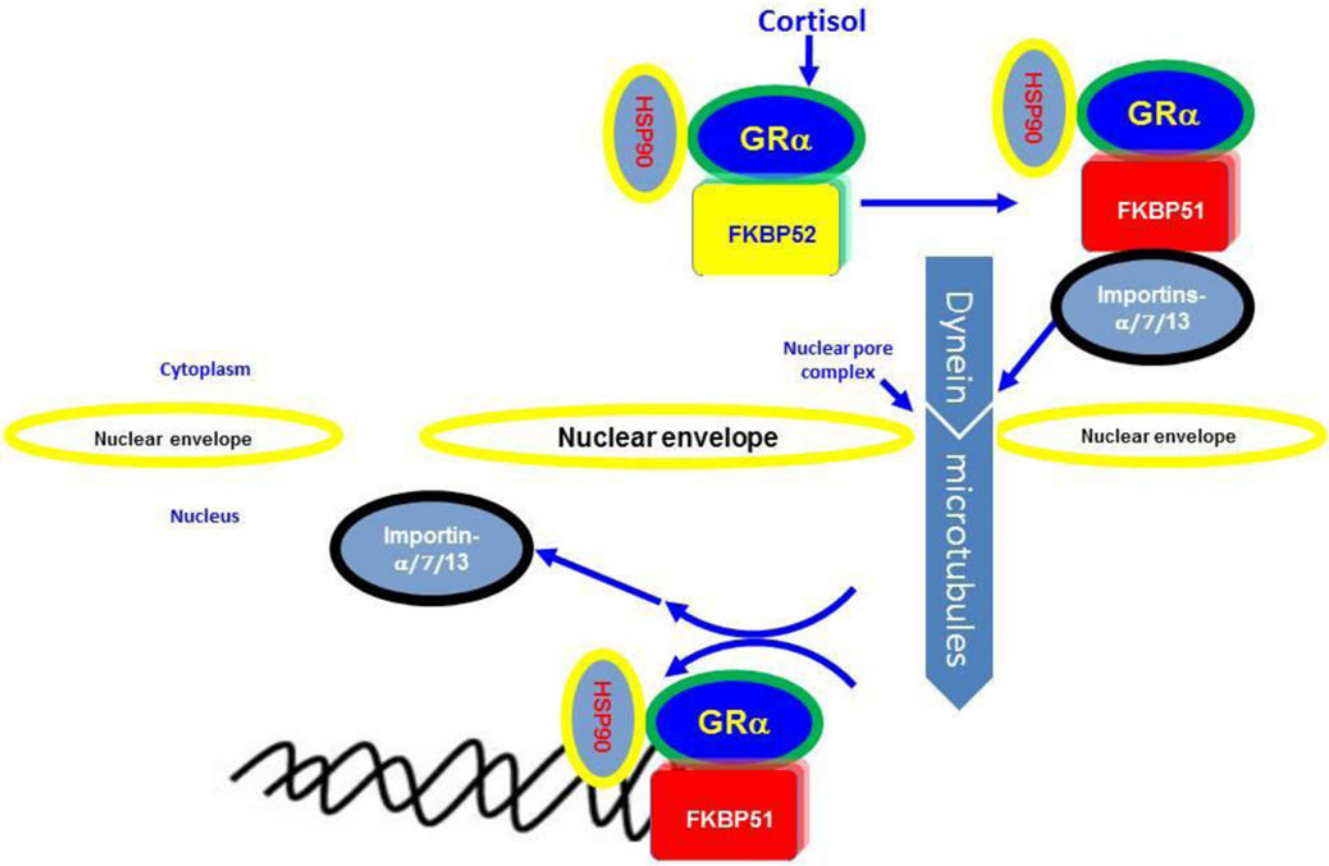


Fig. 1. Proposed model for the nuclear import and the glucocorticoid receptors α and β

FKBP51 is involved in hormone-independent transport of both GRα and GRβ. However, FKBP52 is hormone-dependent and transports only GRα. Importins a, 7, and 13 are involved in GRα-nuclear import.

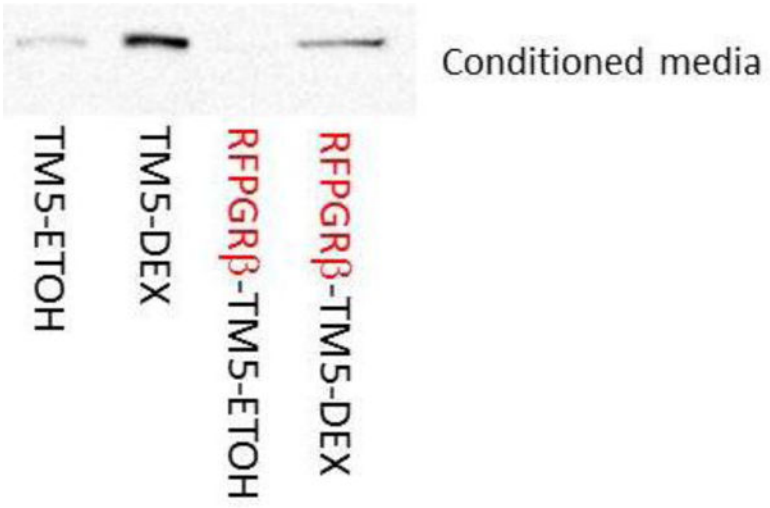
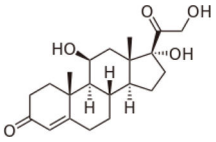
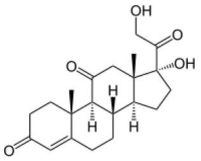
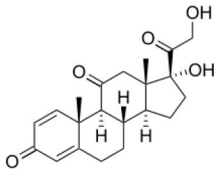
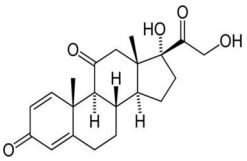
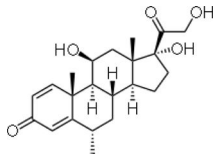
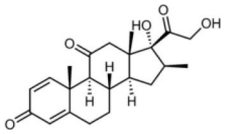
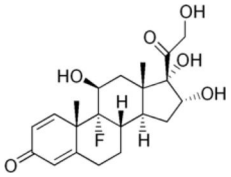


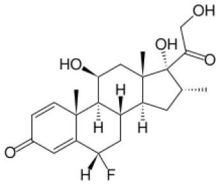
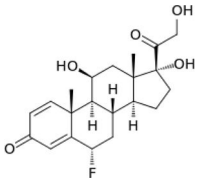
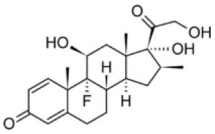
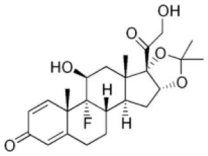
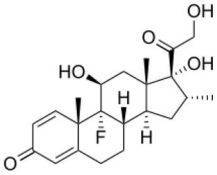
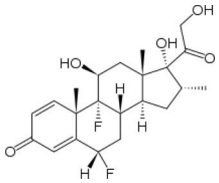
Fig. 2. DEX-induced expression of plasminogen activator inhibitor-1 (PAI-1) is inhibited in RFP-GRβ overexpressing TM5 cells

TM5, a normal transformed human trabecular meshwork cell-line, was treated with DEX (100 nM) for 24 h. Conditioned medium was collected for western blot. Experiments were performed in triplicates ($n = 5$).

Table 1

Relative potencies of commonly used corticosteroids (Chrousos 2012).

Agent	[a]Relative glucocorticoid activity (Anti-inflammatory)	Duration of action (hours)	Transcortin binding	Structure
Cortisol (hydrocortisone)	1	S	++++	
Cortisone	0.8	S	−	
Prednisone	4–5	S	+++	
Prednisolone	5	S	++	
Methylprednisolone	5	S	−	
Meprednisone	5	S	−	
Triamcinolone	5	I	−	

Agent	[a]Relative glucocorticoid activity (Anti-inflammatory)	Duration of action (hours)	Transcortin binding	Structure
Paramethasone	10	I	−	
Flupredinsolone	15	I	−	
Betamethasone	25–40	L	−	
Triamcinolone acetonide	30	I	−	
Dexamethasone	30	L	−	
Flumethasone	120	L	−	

S= short (~12 hr.), I=intermediate (~24 hr.), L=Long (~ 48–72 hr.).

[a]Relative to cortisol.