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Literature Reviews

The Effects of Glucocorticoids on Trabecular Meshwork and its Role in Glaucoma

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Abstract: Primary Open-Angle Glaucoma (POAG), an optic neuropathy that is a leading cause of irreversible blindness, has been studied extensively in hopes of better understanding its underlying mechanism. Glucocorticoids (GC) are commonly used to treat inflammatory ocular conditions but are also known to increase the risk of glaucoma by raising Intraocular Pressure (IOP) in susceptible individuals, leading to steroid-induced glaucoma. Based on clinical studies as well as molecular experiments, steroid-induced glaucoma and POAG show many similarities, including a common underlying mechanism of IOP elevation. Studying steroid-induced glaucoma can reveal more about the pathways underlying decreased outflow of aqueous humor and POAG. GCs have been shown to cause numerous structural changes in the Trabecular Meshwork (TM), including thickening of trabecular beams, activation of TM cells and increased deposition of extracellular material. GCs also upregulate the expression of MYOC (myocilin) in human TM, a gene whose mutation is linked to 10% of juvenile glaucoma cases. Other studies demonstrate that GCs downregulate PLAT, which codes for tissue Plasminogen Activator (tPA) and decrease Matrix Metalloproteinase (MMP) gene expression. In addition, tPA administration has been shown to prevent GC-induced IOP elevation in sheep eyes. The present review demonstrates some of the important interactions between GCs and the TM that can lead to novel therapeutic measures in the setting of steroid-induced glaucoma as well as POAG.

Keywords: Glucocorticoids, Glaucoma, Trabecular Meshwork, Steroid-Induced Glaucoma

Introduction

Primary Open-Angle Glaucoma (POAG) is an optic neuropathy that currently stands as one of the leading causes of irreversible, yet preventable, blindness in the world (Quigley, 1996). Elevated intraocular pressure (IOP) is a major modifiable risk factor for POAG as well as its progression. It is believed that IOP rises when aqueous humor drainage from the anterior chamber through the Trabecular Meshwork (TM), located at the corneal-iridial junction, is impaired (Larsson *et al*., 1995). It is currently unknown exactly how the TM modulates outflow of aqueous fluid, but it is believed to involve the balance between breakdown and synthesis of Extracellular Matrix (ECM) by TM cells. Factors that regulate aqueous humor outflow and ECM remodeling are of great interest to researchers, as this information would allow for better control of IOP and therefore novel treatments of ocular hypertension, steroid-induced glaucoma and POAG.

Glucocorticoids (GC) are commonly prescribed pharmacological agents, often used to treat inflammatory eye etiologies, which are known to increase the risk of glaucoma by raising IOP in susceptible individuals. Studies have shown that about one-third of the population can be classified as “moderate responders,” defined as having an IOP between 20 and 31 mm Hg or a pressure rise of 6-15 mm Hg above baseline with topical application of glucocorticoids (Armaly and Becker, 1965). An additional 4-6% of the population are “high responders,” in whom steroid application leads to a rise in IOP of greater than 15 mm Hg above baseline (Becker, 1965). Those at the greatest risk of responding to steroids are patients with POAG as well as those with known risk factors for glaucoma, which include

advancing age, increased IOP, family history and African-American race. In addition, steroid-responders are more likely to develop POAG than those who are unaffected by GC administration (Lewis *et al*., 1988). Studies show that approximately 90% of patients with POAG experienced an IOP elevation greater than 6 mm Hg after receiving topical 0.1% dexamethasone for 4 weeks (Armaly, 1963). In addition, studies demonstrate that POAG patients have elevated levels of the endogenous glucocorticoid, cortisol, in their serum as well as in the aqueous humor compared to age-matched subjects without POAG (Ray *et al*., 1977; Rozsival *et al*., 1981; Schwartz *et al*., 1987).

Although the exact mechanism of steroid-induced IOP elevation is unknown, it is thought to result from increased aqueous humor outflow resistance at the trabecular meshwork through various biochemical and morphological changes (Rohen *et al*., 1973). Based on clinical studies as well as molecular experiments, it is believed that the mechanism of increased IOP in steroid-induced glaucoma and POAG have many similarities. Studies involving steroid-induced glaucoma can reveal more about the molecular pathways underlying decreased outflow and POAG as well as introduce novel treatment for glaucoma. This review focuses on the studied effects of GCs on TM morphology, MYOC expression and PLAT and MMP expression.

Changed Morphology/Increased Depositions within the Trabecular Meshwork

Trabecular meshwork cells undergo numerous structural changes upon treatment with GCs, which further supports the theory that steroids increase the resistance of aqueous humor outflow leading to increased IOP. TM cells express glucocorticoid receptors and change morphology by increasing their nuclear size and DNA content when Glucocorticoid Receptors (GR) are activated by GCs (Weinreb *et al*., 1983; Wordinger and Clark, 1999). Steroid-induced glaucoma eyes show a fingerprint-like arranged material resembling basement membrane as well as an abnormal accumulation of dense fine fibrils beneath the inner wall endothelium of Schlemm's canal (Johnson *et al*., 1997). In rabbits, steroid-induced TM changes include thickening of trabecular beams, activation of TM cells and increased deposition of extracellular material (Francois *et al*., 1984). In addition, GC treatment in rabbits modifies the composition of TM glycosaminoglycans with decreased hyaluronic acid and an increase in chondroitin sulfate and GAGase resistant material (Knepper *et al*., 1978).

Other studies have demonstrated that dexamethasone (DEX) treatment increases protein levels of zonula occluden-1 (ZO-1) and connexin43 (Cx43), modifies the F-actin architecture and promotes cross-linked actin network formation (Zhuo *et al*., 2010). These changes were more pronounced in glaucomatous TM cells compared to age-matched controls. Cytoskeleton and junctional proteins modify cellular contractility and volume, indirectly generating forces that influence aqueous resistance by controlling intracellular spaces (Zhuo *et al*., 2010). When actin architecture becomes more disorganized upon GC treatment, aqueous outflow resistance increases and TM-ECM interactions becomes altered (Clark *et al*., 2005).

Additional studies have demonstrated that DEX treatment plays a role in increased Cross-Linked Actin Network (CLAN) formation by increasing laminin-5 deposition within the ECM (Filla *et al*., 2014). Although the exact function of CLANs are unknown, they are found with increased frequency in the TM of glaucoma patients (Hoare *et al*., 2008). Syndecans, which are a four-member family of transmembrane heparan sulfate proteoglycans (HSPG), contain extracellular domains that bind ECM proteins and other extracellular ligands. Novel studies show that laminin 5-derived PEP75, which binds to syndecan-4, activates a novel PKCε-signaling pathway that triggers CLAN formation (Filla *et al*., 2014). However, it is unknown whether these changes result in reorganization of the ECM that leads to increase outflow resistance or they are a stress response to increased IOP.

Studies have also shown that glucocorticoid treatment of TM cells decreases their phagocytic abilities and alters their prostaglandin metabolism (Wordinger and Clark, 1999). These post-GC treatment changes include a decrease in the major arachidonate metabolites $PGF_{2\alpha}$ and PGE_2 (Shaw *et al*., 1993), which may contribute to increased IOP secondary to the reported hypotensive properties of prostaglandins in the eye (Camras, 1996). In addition, the TM cells are known to have phagocytic properties, necessary to eliminate debris and maintain the aqueous outflow pathway (Buller *et al*., 1990). Studies show that both glaucomatous as well as normal TM cells treated with DEX have decreased phagocytic capabilities, with glaucomatous cells showing a much greater decrease in their phagocytic abilities (Zhang *et al*., 2007). It has been proposed that the differential decrease in phagocytic activity is mediated by reduced expression of GRβ, an alternatively spliced variant of the GR, in glaucomatous TM (Zhang *et al*., 2007).

MYOC

One of the four known genes that are associated with glaucoma, MYOC (myocilin/*TIGR*), has been studied significantly in hopes of elucidating more about the molecular and cellular mechanisms of the disease. MYOC is a secreted glycoprotein that accumulates in the cell when mutated, which occurs in

10% of juvenile open-angle glaucoma cases and in 3-4% of adult onset POAG cases (Fingert *et al*., 1999; Kwon *et al*., 2009; Stone *et al*., 1997). It is expressed in numerous tissues in the eye, including the trabecular meshwork, iris, ciliary body, sclera, choroid, cornea, lamina cribosa, retina and optic nerve (Adam *et al*., 1997; Kubota *et al*., 1997; Ortego *et al*., 1997; Ricard *et al*., 2001; Tamm *et al*., 1990).

Studies have demonstrated that MYOC expression is increased in hTM cells 7-10 days after continuous treatment with glucocorticoids (Nguyen *et al*., 1998; Polansky *et al*., 1997). This suggests that the MYOC changes are a secondary response of GC treatment. This is also supported by the finding that DEX-induced MYOC induction can be blocked by the protein synthesis inhibitor Cycloheximide (CHX) (Shepard *et al*., 2001). Some studies report that multiple Glucocorticoid Response Elements (GRE), which serve as binding regions for Glucocorticoid Receptors (GR), are found within 2700 bp of the *MYOC* 5′-flanking region (Shepard *et al*., 2001). However, other studies did not identify any GREs from the *MYOC* translation start site to 1900 bp upstream (Fingert *et al*., 1998) and did not demonstrate any MYOC promoter induction by dexamethasone (DEX), possibly indicating the lack of GRE involvement in the DEX-MYOC interaction (Shepard *et al*., 2001).

Further investigation into this steroid-induced change revealed that calcinerin inhibitors can reduce the dexamethasone increase in MYOC expression, implicating calcinerin involvement in MYOC-steroid pathway (Faralli *et al*., 2015). The known relationship between calcinerin and the cytoplasmic Nuclear Factor of Activated T cell (NCATc) in the activation of T-cells lead to further studies which demonstrated that a reduction in NCATc1 mRNA levels attenuated the DEX-induced increase in *MYOC* transcription (Faralli *et al*., 2015). DEX was also shown to cause translocation of NCATc1 into the nucleus of hTM cells (Faralli *et al*., 2015). Further studies concluded that DEX activates the calcineurin/NFATc1 pathway in a calcium independent mechanism (Faralli *et al*., 2015). Although further research must be carried out to determine how exactly DEX activates the calcineurin/NFATc1 pathway, inhibitors of the pathway can be beneficial in the treatment of steroid-induced glaucoma and POAG.

PLAT

Various studies focus on the involvement of GC interaction with PLAT, the gene encoding for tissue Plasmingoen Activator (tPA). TPA is a serine protease, largely known for its clot breakdown capabilities through the activation of plasminogen to plasmin, which degrades fibrin (Lijnen and Collen, 1995). It has been demonstrated that tPA, or other downstream proteins, can also activate pro-matrix-metalloproteinases (MMPs) to their active form, which are then responsible for the degradation and maintenance of the ECM, ultimately affecting outflow and IOP (Murphy *et al*., 1992).

Studies demonstrate that GC changes include the downregulation of PLAT, as well as the inhibition of MMP gene expression in the TM (Kumar *et al*., 2013a). It is thought that the decreased expression of MMPs can lead to the accumulation of various components and debris in the ECM, leading to increased outflow resistance. This outflow resistance has been demonstrated by treating mice with Triamcinolone Acetonide (TA) and recording outflow facility, which is significantly reduced in the TA-treated group compared to controls (Kumar *et al*., 2013b). Furthermore, PLAT upregulation has been shown to reverse the increase in outflow resistance induced by GCs in mouse eyes (Kumar *et al*., 2013a). However, it is still unclear exactly which pathway is responsible for the upregulation of MMPs and whether it is plasmin-dependent.

Sheep IOP can be elevated with topical steroid administration and continues to remain elevated for 1-3 weeks after the discontinuation of the agent (Gerometta *et al*., 2009). It was shown that intravitreal administration of human recombinant tPA in this sheep model of GC-induced ocular hypertension led to sustained pressure reduction compared to control animals (Gerometta *et al*., 2013). In addition, an adenoviral vector containing GC-inducible human MMP-1 cDNA was able to protect against and reverse the IOP elevated caused by steroid treatment in sheep eyes (Gerometta *et al*., 2010). The tPA and MMP counter-activity against steroid-induced glaucoma holds a lot of promise but further research must be performed to determine other key factors involved in these pathways.

Glucocorticoid Receptor Isoform GRβ

Another subset of research involving steroid induced glaucoma focuses on alternative GR splicing and its role in steroid responsiveness. GRβ, the lesser-known splice variant, which differs from GRα with a variation at the carboxyl termini, can act as a dominant negative inhibitor of GRα activity (Oakley *et al*., 1996). This splice variant is shown to play a role in various steroid-resistant entities such as asthma and rheumatoid arthritis (Sousa *et al*., 2000; Derijk *et al*., 2001). Dexamethasone treatment of both normal and glaucomatous TM cells results in a shift of GRα from the cytoplasm to the nucleus, which does not occur with GRβ after steroid treatment (Zhang *et al*., 2005). This demonstrates the lack of GRβ susceptibility to steroids. The potential involvement of GRβ in steroid responsiveness is further supported by studies that demonstrate that TM cells from glaucomatous eyes express lower levels of GRβ than their controls. In the same study, it was shown that

glaucomatous TM cell lines are more susceptible to GC induction of a GRE reporter gene (Zhang *et al*., 2005). Higher GRβ expression in normal TM cells could make TM more resistant and therefore glaucomatous TM cells more responsive, to the effects of GCs. This study demonstrates the potential mechanism for enhanced glucocorticoid responsiveness in POAG, supported by the finding of decreased GRβ expression in glaucomatous TM and the ability of GRβ to attenuate GRα activity in TM cells.

Conclusion

As many studies have demonstrated, steroid-induced glaucoma and POAG show many similar features, both clinically and on the molecular level. GCs have been used extensively in the laboratory and in various animal models to induce glaucoma and study the underlying mechanisms of IOP elevation. GC effects on gene expression, including MYOC, PLAT and MMPs has opened up new avenues of exploration for pathways that are involved in regulation of aqueous outflow. Other studies focus on physical changes that take place in the TM when it is exposed to GCs, such as modifications in the composition of TM glycosaminoglycans, increased CLAN formation and increased deposition of extracellular material. Further work must be carried out to better elucidate these changes and define the exact molecules that are directly and indirectly involved in IOP elevation. For example, the mechanism responsible for higher levels of GRβ in normal TM as compared to glaucomatous TM would lead to a possible intervention that would allow for the upregulation of GRβ resulting in a greater resistance to the effect of GCs on a molecular level. Similarly, elucidating the pathway by which tPA decreases aqueous outflow resistance will provide the opportunity to intervene clinically in patients with steroid-induced glaucoma, as well as POAG if these mechanisms are also underlying concepts in the pathogenesis of POAG. Although some studies show the involvement of MMPs in the tPA-mediated decrease of aqueous outflow resistance, whether this is a plasmin-mediated event and what other proteins are involved in this process is still unknown. Further experiments must be performed to better define these pathways and get closer to a safe, clinical intervention for glaucoma, whether steroid-induced or POAG. Using GCs to study glaucoma can lead to a better understanding of its causes as well as novel therapeutic interventions for both POAG and steroid-induced glaucoma.

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Ethics

There are no ethical issues that may arise after the publication of this manuscript.

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