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Review Article

Could Mineralocorticoids Play a Role in the Pathophysiology of Open Angle Glaucoma?

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Since the pathomechanisms of primary open angle glaucoma are still not defined, different aspects related to this topic have to be discussed and further investigated. Possible candidates are the mineralocorticoids, which are known to lower intraocular pressure. A data search and personal investigations assume a limited role of mineralocorticoids for the development of glaucoma. Specific experiments for a final conclusion are, however, not yet performed.

1. The Present Defined Risk Factors for Open Angle Glaucoma Are Poor

Glaucoma comprises a number of different pathomechanisms leading to a specific degeneration of the retinal ganglion cells and changes in the optic nerve head. Primary open angle glaucoma is the most common form and affects about 1% of the western population.

To date, the only defined risk factors for the development of primary open angle glaucoma (POAG) are age and elevated intraocular pressure (IOP). Both factors are complex and their precise role and regulation are not known. Pathomorphological correlations discussed for the elevated IOP are the appearance of "plaque-like extracellular material" in the human trabecular meshwork [1, 2], "empty spaces/giant vacuoles" in the juxtacanalicular region next to Schlemm's canal [3–5], and the size of Schlemm's canal itself [6, 7]. The active role of TM cells in this regulative process was considered due to their contractile properties [8, 9] and due to intracellular volume regulation [10–12]. Interestingly, the increased production of aqueous humour alone seems not to be responsible for elevated intraocular pressure, although a number of therapies modify this input.

In recent years, a broader understanding of intracellular volume regulation was gained by the description and investigation of specific ion channels and their molecular regulation. In this context, corticoid hormones played a crucial role [13, 14]. This paper tries to bring this knowledge forward to glaucoma pathophysiology.

2. Glucocorticoids Are Known for Their Ocular Hypertensive Property

Early investigations of steroid hormone function in the eye were lead by clinical observations of IOP elevation in one-third of the population after topical cortisone treatment [15, 16]. Persisting ocular hypertension can lead to a specific type of open angle glaucoma, the "cortisone-induced" glaucoma [17, 18] with a typical morphological appearance [19, 20]. Interestingly, systemic elevation of cortisone can slightly increase IOP but does not lead to a higher risk of glaucoma development [21]. Therefore, local mechanisms seem to play a crucial role. One of them is the 11β-hydroxysteroid dehydrogenase (HSD) consisting of two isozymes with distinct different functions. HSD1 is the key enzyme for activation of cortisone; HSD2 leads to inactivation of cortisone in specific tissues with aldosterone receptors which could also be activated by cortisone. To postulate an effect of cortisone, HSD1 for activation and the glucocorticoid receptor (GR) should both be present. In the trabecular meshwork GR and HSD1 were described originally [22], but subsequent studies only confirmed the presence of GR [23, 24]. From

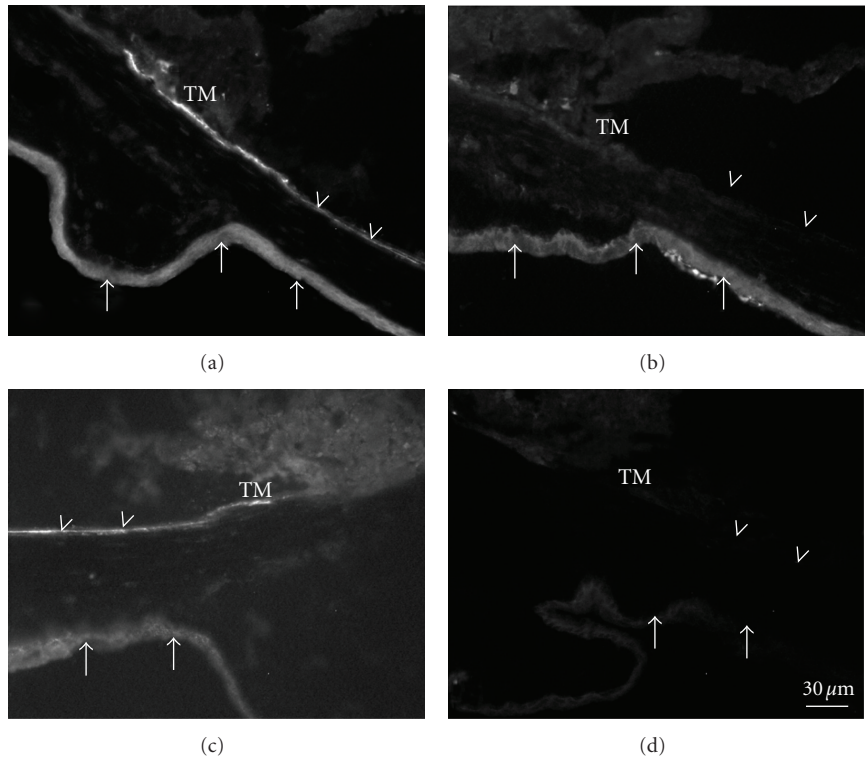

Figure 1: Immunohistochemical staining of the mouse anterior segment with antibodies against α-ENaC (a), β-ENaC (b), and γ-ENaC (c), immune sera were kindly provided by Bernard Rossier and Christoph Korbmacher, and without primary antibody (d). Note the intense staining of the trabecular meshwork (TM) and corneal endothelium (arrowheads) with α- and γ-ENaC, but not with β-ENaC. Arrows: conjunctiva and cornea epithelium. The conjunctiva did not show staining with antibodies against γ-ENaC (arrows in (c)).

a functional point of view, glucocorticoids lead to an intracellular volume increase in trabecular meshwork cells [25–27] and modify the extracellular matrix production [28, 29]. Most surprisingly, one of the extracellular matrix proteins affected is elevated in all human glaucomatous donor eyes [30, 31], but physiological studies recently questioned its role for elevation of trabecular meshwork resistance and IOP [32, 33]. Thus the cellular volume increase effect of cortisone has the best evidence to be of pathophysiologic relevance for IOP increase at present.

3. Mineralocorticoids Have Some Effects in the Eye

For a long time, a second group of corticoid hormones, the mineralocorticoids, were not considered to play any significant function in the eye [34]. However, early investigations mentioned that the aldosterone-antagonist spironolacton led to a decrease of intraocular pressure in glaucomatous patients [35]. Mirshahi and coworkers were the first to describe mineralocorticoid hormone receptors (MR) in the retina and all epithelial cells of the eye [36, 37]. To consider specific aldosterone function, the presence of HSD2 next to the MR is necessary. The presence of MR and HSD2 in the trabecular meshwork is described controversially [22–24]. Mineralocorticoid effects are thought to be mediated by epithelial sodium channels (EnaC) [38, 39], which are also present at numerous places in the anterior eye segment [40–43]. These channels might serve two different functions: one is fluid secretion from the ciliary epithelium (increase of aqueous humour formation), and the other is regulation of the trabecular meshwork resistance by volume regulation of the trabecular meshwork cells. The first is the most widely suggested mechanism for aldosterone [44] since a consistent presence of MR and a strong evidence for the presence of HSD2 are reported in ciliary epithelium cells [22–24]. If the trabecular meshwork is also a target tissue for aldosteron remains to be determined.

4. Can Mouse Eye Models Help Concerning Mineralocorticoid Effects?

A number of mouse models were established to study mineralocorticoid effects but no data exists about the eyes of these animals. The existing genetically altered mice show either an overexpression of the MR [44–46], a knockout of HSD2 [47], or alterations of the ENaC ion channels (Liddle's syndrome) [48, 49].

Unfortunately, there is no data in mouse eyes for the presence and distribution of MR and HSD2. Personal investigations on the distribution of ENaC in the mouse anterior eye segment showed intense staining for α- and γ-EnaC, but no staining for β-EnaC in the trabecular meshwork, while the ciliary epithelium showed only a weak staining reaction (Figure 1).

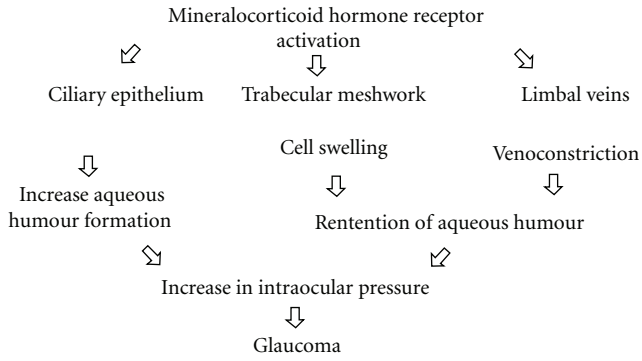

Figure 2: Proposed mechanisms by which mineralocorticoids play a role in glaucoma.

Overexpression of MR was induced in B6D2 animals. During embryogenesis, MR overexpression led to massive changes in the anterior eye chamber due to epidermal atrophy in these nonviable puppets [46]. Unfortunately, these animals have a DBA/2J background leading to changes in the chamber angle beginning at 3 months of age. Personal investigations on the eyes of 6-months-old transgenic animals (P1.hMR and P2.hMR from [44, 45]) show massive synechiae of the iris, atrophy of the ciliary body, strong pigmentation of the chamber angle, and loss of retinal ganglion cells. These findings match with findings observed in other DBA strains [50–52]. Specific mineralocorticoid related changes could not be observed. Knockout of HSD2 was performed in C57/Bl6 mice.

The mouse model established for Liddle's syndrome has an altered β-EnaC subunit. There seems to be no effect of aldosteron on the α-EnaC subunit in these animals [53]. Personal investigations on eyes of these animals revealed a normal morphology. Schlemm's canal was widely open, trabecular meshwork cells were not swollen, abnormalities in the anterior and posterior eye segments could not be detected. Since the normal mouse eye does not express the β-EnaC subunit in the trabecular meshwork and inner eye surfaces, these results are not surprising.

Concluding, at this stage of research mouse models do not help to answer questions related to the role of mineralocorticoids in the eye.

5. Specific Mineralocorticoid Dysfunctions Also Exist in the Human: How about Ocular Pathology in These Patients?

A number of conditions are known in the human associated with mineralocorticoid dysfunction. A relation to ocular pathologies was tested.

Hyperaldosteronism is a common, but rarely diagnosed condition (estimated 1.5–3.5% of the entire population in Germany [54]). The induced high blood pressure can affect the eye but not in a glaucoma-specific way. There are no functional changes in the eye related to this general condition. It remains to be determined if these patients show any association to glaucoma.

Apparent mineralocorticoid excess is a condition with lack of HSD2 and subsequently increased activation of MR [55]. There is no report in the literature that any of the diagnosed patients suffered from either elevated IOP or glaucoma.

Pseudohypoaldosteronism type 1 is related to a reduction of alpha ENaC function [56, 57]. A communication with Prof. Hanukoglu (Tel Aviv) revealed that these persons do not complain of any specific eye symptoms. An extended ocular examination of his oldest patient at that time (19 years old) showed normal intraocular pressure (17 mmHg), a normal anterior chamber including the chamber angle, and a normal OCT of the nerve fibers in the retina. The only finding was a slightly increased corneal thickness (570 μm). If this finding is related to a reduced function of the corneal endothelium remains to be determined.

6. Is There Any Mineralocorticoid Input to Glaucoma Pathophysiology at Present?

Systemic application of mineralocorticoids to glaucoma patients shows no changes in the IOP in most of the cases [58, 59]. However, single individuals react with a high increase in intraocular pressure [58]. Unfortunately, these "mineralocorticoid-sensitive" persons are not further characterized. They could constitute a new subgroup of ocular hypertension or glaucoma patients, but more clinical data has to be collected to define these persons.

The lack of general agonist effects combined with the mild IOP decrease of antagonists [35] points to a possible role of mineralocorticoids for glaucoma therapy but not for general glaucoma pathophysiology. The narrowed role is also supported by the negative findings in the animal models and the various human conditions described above. The therapeutic effect of mineralocorticoid antagonists seems mainly mediated by a decrease of aqueous humour formation [36]. If there is some effect on the outflow pathway remains open.

One additional aspect of mineralocorticoid function is venoconstriction and thus an increase in postcapillary pressure [60, 61]. Venoconstriction could also be of relevance for elevated intraocular pressure as known from rat glaucoma models [62]. If mineralocorticoid mediated venoconstriction is also present in limbal veins remains to be determined. A different venous sensitivity could be a criterion for the above hypothesized mineralocorticoid-sensitive subgroup of humans.

7. Conclusion

The proposed mechanisms by which mineralocorticoids play a role in glaucoma are summarized in Figure 2. While there is some evidence that the ciliary epithelium is affected by mineralocorticoids, the role of the trabecular meshwork cells and of the limbal veins remains to be determined. Hopefully this paper attracts more scientists and clinicians for further research in the area of mineralocorticoids with respect to the pathogenesis of glaucoma.

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