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The renin-angiontensin system and the development of new antiglaucoma medications

O sistema renina-angiotensina e o desenvolvimento de novos medicamentos antiglaucoma

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Dear editor;

We have read the article entitled "Aqueous humor renin, angiotensin I, and angiotensin II activity in primary open-angle glaucoma"[1] published in this esteemed journal. We would like to commend the authors because this is a well-written article with an extremely relevant theme. Additionally, we would like to raise few points regarding this study.

The selection of study participants could have followed specific exclusion criteria. The use of oral beta-blockers is known to weaken the response of intraocular pressure reduction when used concomitantly with beta-blocker eye drops for the treatment of glaucoma[2]. In addition, the use of beta-blocker eye drops in most participants with primary open-angle glaucoma may have influenced the final result of the concentration of renin being lower in the aqueous humor of participants with cataract and glaucoma than in the control group (i.e., patients with cataract only). The results presented by the authors contradict the current literature. Thus, for the intervention, it is best to withdraw treatment with beta-blocker eye drops for 15 days before collecting the aqueous humor. In cases where it is not possible to completely withdraw the medication, the beta-blocker eye drops can be substituted for another class of antiglaucomatous eye drops which does not directly interfere with renin activity.

Other important aspects that were not considered in the article are the participants' stage of glaucoma and the number of topical medications for glaucoma that each participant was using at the time of the research. The ethnicities of the study participants were also not taken into account. This is important because black patients, for example, respond less to angiotensin-converting enzyme (ACE) inhibitors than white hypertensive patients. Furthermore, antihypertensive medications have similar dose-related effects among both black and white patients, but these are achieved at higher doses in the former[3]. Therefore, the doses of antihypertensive medications should also have been considered.

Angiotensin II has been implicated in retinal vascular diseases, such as retinopathy of prematurity and diabetic retinopathy, and recent studies on its relationship with neovascularization and glaucoma have emerged[4]. The reduction in angiotensin II production promoted by ACE inhibitors achieves a similar effect to beta-blockers, which reduce the activity of plasma renin[5]. It is up to us researchers to determine if the renin-angiotensin system is indeed involved in the pathogenesis of glaucoma, and, if possible, eventually develop new antiglaucoma medications with ACE inhibitors.

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Response: Comments on The renin-angiotensin system and the development of new antiglaucoma medications

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We would like to thank Aline R. P. Coelho and colleagues[1] for their comments on our recent article, which evaluated the aqueous humor (AH) renin, angiotensin I, and angiotensin II activities in primary open-angle glaucoma (POAG). Our study has presented innovative findings displaying a remarkable reduction in AH renin activity among patients with POAG under timolol maleate topical treatment[2]. The comments of the authors raise a relevant point; significantly lower AH renin activity observed in patients with cataract and POAG might indeed be contradictory (a point also made in our original manuscript). Since high levels of renin may be implicated in modulating the intraocular pressure in glaucoma[3], most patients with POAG showed lower renin activity than controls because they were using timolol maleate eye drops. Beta-blockers and angiotensin-converting enzyme (ACE) inhibitors may reduce the activity of plasma renin. Nonetheless, both the magnitude of this reduction and its cascade interactions are not entirely understood in the eye.

We agree with Coelho and colleagues that a washout period of beta-blocker eye drops would be ideal, as we have already mentioned in our discussion. However, a washout protocol should be clinically avoided since all included patients presented with severe POAG. They were under the maximum tolerated medication (hindering a drug switch) and even indicated for filtering surgery.

Although some of the local renin-angiotensin system (RAS) factors depend on interactions with circulatory RAS to fully operate, in some tissues, RAS may do it independently[4]. We agree that more information on race and oral medical treatment, including ACE inhibitors, is desired. However, the evidence of differential effects of antihypertensive medications in black patients as well as the local effect of systemic antihypertensives have not been completely studied in the eye. Furthermore, as presented in Table 1 of the manuscript, only a few patients across both groups were under systemic ACE inhibitors, and significantly fewer patients with POAG were treated with systemic beta-blockers.

Few studies have shown conditions that decrease AH renin activity. Neither a local increased consumption of renin nor its preferential bond switch to the prorenin receptor and consequent activation of this alternative RAS pathway have been studied in the eyes of patients with glaucoma. Since timolol maleate eye drops may reduce AH renin activity, the roles of renin and other RAS factors should be thoroughly investigated in various forms of the disease, including the study of different ocular target tissues, such as the trabecular meshwork. Further studies will help us fully understand the relationship between systemic and ocular RAS factors in glaucoma.

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