Letter to the editor from Behar-Cohen, et al: "The Cortisol Response of Male and Female Choroidal Endothelial Cells: Implications for Central Serous Chorioretinopathy"

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Disclosure statement: FBC, MZ and FJ have been cited as inventors on 2 patents belonging to public institutions, on the use of mineralocorticoid receptor antagonists for the treatment of macular edema and choroidal neovascularization.

Dear Doctor Brinks,

We have read with interest the paper of Joost Brinks et al 2021 Sep 21;dgab670. doi: 10.1210/clinem/dgab670.Online ahead of print, entitled The Cortisol Response of Male and Female Choroidal Endothelial Cells: Implications for Central Serous Chorioretinopathy (CSCR).

In this paper, the authors failed to identify the mineralocorticoid receptor (MR) in endothelial cells from the choroid of human eyes collected around 24 hrs after death.
The authors missed the important information, published 10 years ago by the team who developed the antibody they have used, that the mineralocorticoid receptor (MR) is unstable.
Indeed, the team of Gomez-Sanchez explains that to use the antibody and detect MR, "prompt handling and inactivation of enzymes of degradation is required…..Processing the sample immediately after harvest in a buffer containing protease and phosphatase inhibitors preserves the MR intact…" (1). It was thus expected that MR would be degraded when eyes are enucleated from donors after 24 hrs of death.
The MR immunohistochemistry images shown in this paper supports that MR might have been degraded since the MR signal in the retina is extremely low, without any signal in ganglion cells, in retinal endothelial cells and very scarce signal in few cells the inner retina, which is very different with what has been found by several other authors (2–4). There is no MR signal in the nuclei of any cells in the choroid and no MR signal in the nuclei of retinal pigment epithelial cells either, which is very different from previous results obtained on fresh tissues and cells(5,6). More importantly, the positive MR control do not show any signal in the nuclei, which could indicate methodological issues.
The authors claim that there is no animal model that recapitulate human pachychoroid phenotype but they omitted to cite the P1hMR mouse model (mouse that overexpresses human MR) (6) and the NAS (nephrectomy aldosterone salt) models (7) that show all features of human eyes with pachychoroid.

Due to the lack of similitude between the cellular model used in this study and the human physiologic conditions regarding steroid receptors, this cellular model is useful to decipher the transcriptional regulations of cortisol upon binding to the glucocorticoid receptor (GR) but cannot bring any information regarding human physiological or pathological conditions. The

conclusions on the predominance of GR pathway activation by cortisol in human choroidal endothelial eyes with CSCR is thus misleading.

In addition, it is very unlikely that the veinous vasodilation observed in patients with CSCR could result from a direct activation of corticoid receptors in choroidal endothelial cells because vasodilation in the choroid is under neural control (8). Indeed, many other cells expressing both GR and MR could influence the vascular dynamics such as pericytes, smooth muscle cells, microglia and more importantly neural cells from the autonomous system, that controls the choroidal blood flow regulation.

The analysis of the cortisol response of endothelial cells alone does not allow to draw any conclusion on the involvement of MR or GR pathway in CSCR.

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MR **Negative control**