Is GPR30 the Membrane Aldosterone Receptor Postulated 20 Years Ago?

To the Editor:

Gros et al.1 describe the involvement of GPR30 in rapid actions of aldosterone. The hypothesis that a structure other than the mineralocorticoid receptor (MR) may mediate rapid actions of aldosterone was postulated many years ago. Wehling et al.2 showed in 1991 that the rapid effect of aldosterone on the sodium-proton exchanger in human mononuclear leukocytes and vascular smooth muscle cells was independent of classic aldosterone antagonists like canrenone or canrenoate.3 Grossmann et al.4 showed almost 15 years later that cytosolic Ca\(^{2+}\) was increased by aldosterone in mock- and in human MR-transfected cells to the same extent, and spironolactone did not block this effect, pointing to MR-independent mechanisms. Most recently, aldosterone binding sites were detected at the membrane of human endothelial cells using atomic force microscopy. Aldosterone binding to these sites was spironolactone and dexamethasone insensitive.5 These examples are just a few of those pointing to MR-independent rapid aldosterone actions, and this interpretation is mainly based on their insensitivity to MR antagonists.

The functions of GPR30, especially with respect to estrogen actions, are a matter of ongoing debate, and the new findings on its involvement in rapid aldosterone actions add an important facet to this discussion.

Gros et al.1 postulate that eplerenone and spironolactone are partial antagonists of GPR30. This needs further clarification. Analyzing Figure 2 of the article by Gros et al.1 in detail, it is tempting to assume that, in vascular smooth muscle cells which have been transfected with the control construct (green fluorescent protein), extracellular signal–regulated kinase phosphorylation by aldosterone reflects basic MR expression, because it is completely inhibited by eplerenone. When MR is overexpressed in those cells, the effect of aldosterone is roughly doubled, but it remains completely (\(\approx 100\%\)) eplerenone sensitive. In GPR30-transfected cells, extracellular signal–regulated kinase phosphorylation by aldosterone is also roughly doubled. However, the added effect is not eplerenone sensitive, because eplerenone decreases extracellular signal–regulated kinase phosphorylation only by exactly the same amount seen in cells transfected with the control construct (green fluorescent protein). Therefore, the effect of eplerenone in the GPR30-transfected cells seems to be fully explained by the inhibition of the assumed endogenous MR activity. This is underlined by numerically identical results in Figure 7A through 7C of the article by Gros et al.1 which show identical relations for apoptosis as readout or by Figure 9B in the article by Gros et al.1 for myosin light chain phosphorylation as readout. Figure 3 in the article by Gros et al.1 demonstrates an incomplete inhibition by epilrenone of G1-stimulated responses, as seen in Figure 5A of this article for endothelial cells and aldosterone as an agonist. This interpretation is only flawed by more complete effects of G15 on aldosterone responses in GPR30-transfected cells (Figure 9C of the article by Gros et al.1), which have to remain unexplained. If correct, these interpretations underscore the fact that eplerenone and spironolactone are not antagonists for the rapid action of aldosterone mediated through GPR30.

This interpretation would identify GPR30 as an almost perfect candidate for the membrane aldosterone receptor, which we characterized mainly by its landmark property of resistance to classic MR antagonists more than 2 decades ago. Further studies need to validate GPR30 as an aldosterone receptor and to corroborate our interpretation of the impressive data by Gros et al.1

Disclosures

M.W. received consulting and lecture fees from Pfizer, Roche, Novartis, Lilly, PAION, MorphoSys, 4D-Biomedical, and Daiichi-Sankyo. He is a former employee of AstraZeneca (2004–2006).

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Hypertension is available at http://hyper.ahajournals.org

DOI: 10.1161/HYPERTENSIONAHA.111.170977
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Hypertension. 2011;57:e16; originally published online March 21, 2011;
doi: 10.1161/HYPERTENSIONAHA.111.170977

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0194-911X. Online ISSN: 1524-4563

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World Wide Web at:
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