GPR30, Mineralocorticoid Receptors, and the Rapid Vascular Effects of Aldosterone

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The second salient finding of the studies presented is that both spironolactone and eplerenone, classical MR antagonists, lowered but did not abolish the GPR30-mediated effects of aldosterone on VSMC. The authors term them partial antagonists, a term usually reserved for molecules that are also partial agonists. Eplerenone appears to be a full antagonist under some circumstances (eg, Figures 1B and 3B), as does spironolactone (Figure 3B), but a weaker antagonist under others (Figures 2, 5B, and 7B), with the reason for this discrepancy not apparent. Under no circumstances, however, is there any suggestion that eplerenone or spironolactone has any GPR30 agonist activity, as clearly shown in Figures 3B and 9B. Partial antagonist is therefore a misnomer, and the MR antagonists are thus putatively GPR30 antagonists per se, with the expectation that at higher concentrations the effect will be closer to more complete.

In terms of potential (patho)physiological roles, there are a number of fascinating findings, and one item of unfinished business. First, in a demonstration of the perils of cell culture, the authors clearly demonstrate that GPR30 expression diminishes relatively rapidly with cell passage, necessitating the use of freshly dissociated or transfected cells. Second, they show that whereas MR levels remain relatively constant in passaged cells, in cells transfected to express (probably overexpress) GPR30, MR expression is downregulated. What determines GPR30 levels in vivo, or in freshly isolated aortic VSMCs, is understandably not addressed in the paper, but may be a factor in regulating MR expression in vivo. If this is the case, then GPR30 levels would have a (ligand-independent) flow-on effect on both acute and genomic actions of aldosterone via classical MR, a level of complexity not previously suggested. Finally, given the opposing effects of aldosterone (via GPR30) and estradiol (via ERα, albeit at relatively high concentrations [see Figure 4C]), it is tempting to speculate that these two hormone-receptor systems act as ying and yang in terms of vascular smooth muscle ERK activation, and the consequences thereof.

The unfinished business, which bears heavily on the possible physiological roles of GPR30 as a membrane MR, are the data presented in supplemental Figure 2. Supplemental Figure 2B shows that corticosterone, the physiological glucocorticoid in rats, appears to be a weak agonist in terms of ERK phosphorylation but that the significant increase seen at 100 pM is unaffected by the GPR30 antagonist G15. This is unfinished business because while it shows corticosterone not to be a GPR30 agonist in terms of ERK phosphorylation, it throws no light on whether it might be a GPR30 antagonist (as it is for MR in the kidney when 11β-hydroxysteroid...
If corticosterone proves to be a GPR30 antagonist, the picture is more complex, but the cause not lost. Circulating free concentrations of physiological glucocorticoids are ≈100 times those of aldosterone, so that under normal circumstances only ≈1% of the vascular GPR30 would be occupied by aldosterone, if the affinity of the receptor is similar for both steroids. This is the case for classical MR in tissues such as cardiomyocytes, which do not express the enzyme 11β-hydroxysteroid dehydrogenase. This notwithstanding, only modestly elevated aldosterone levels (but inappropriate for salt status) have clearly been shown to have deleterious effects, for example in patients with primary aldosteronism, even before the onset of hypertension.6 Clearly there are circumstances that either allow aldosterone increased access to nonprotected MR, sufficient to set in train its deleterious effects, or, in the context of tissue damage, allow MR activation by glucocorticoids.5 If corticosterone is under normal circumstances a GPR30 antagonist, it is similarly possible that in certain pathophysiologic conditions it becomes an agonist, as it does for classical MR.

A final word on the last clause of the abstract in this Gros et al1 paper, which reads “…but also suggest alternative therapeutic strategies for modulating aldosterone actions on the vasculature in vivo.” The authors extend this statement not in the Discussion but in the single-sentence Perspectives section, by the intriguing conclusion that “The present studies provide evidence that acute effects of aldosterone on VSMC contractility and apoptosis rely on both MR- and GPR30-dependent pathways and suggest that agents targeting each of these receptors may provide differential levers to modulate aldosterone actions in different pathological states.”

In terms of effects on vascular smooth muscle, this is intriguing but not supported by any of the data in the paper: in this tissue, aldosterone has equivalent effects via both MR and GPR30, so that no basis for the use of antagonists selective for one of the other receptors is evident. In contrast, in endothelial cells, the authors find GPR30 but not MR: if the endothelial cell cross-talks with the VSMC (see Figure), for which there is ample precedent, it might be suggested that this is a suitable point of attack for GPR30-specific agents. There are several caveats to this: (1) such agents are unlikely to be endothelial cell specific and (2) endothelial cells in other species may express MR.

Perhaps the most likely therapeutic advance would reflect leveraging off the eplerenone/spironolactone findings in the paper by Gros et al.1 Although there are no dose-response data, it is possible that eplerenone is in fact a GPR30 antagonist with a similar IC₅₀ value to that for MR. Such crossover is not without precedent: at least one of the calcium channel blockers has modest but at high dose possibly clinically significant effects via MR.7 If spironolactone is a generation 1 MR antagonist and eplerenone is generation 2, then perhaps an agent with a low IC₅₀ for both MR and GPR30 will be found among the suite of generation 3 (gen3) candidates currently under development (gen3: as potent as spironolactone, as specific as eplerenone, nonsteroidal, cheap to manufacture, long patent life) or, more probably given the current fears of hyperkalemia, generation 4 (gen3 plus a measure of renal tubule sparing).

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**Figure.** Hypothetical pathways for effects of aldosterone (aldo) via membrane-located GPR30 and intracellular MR. EC indicates endothelial cell; N, nucleus; VSMC, vascular smooth muscle cell.

dehydrogenase is operant,2,3 or in the normal but not the damaged cardiomyocyte4,5).

It is thus crucial, before a full consideration of potential (patho)physiological roles for GPR30 as a membrane-bound aldosterone receptor, for its affinity for corticosterone to be determined and its potential as a GPR30 antagonist to be established (or ruled out) by appropriate dose-response studies (10 pM aldosterone, alone and plus 10 pM-1 µM corticosterone). If corticosterone does not block the effect of aldosterone, the path is clear. Here we have what appears to be an inherently aldosterone-selective receptor, with both rapid effects and the potential, in a curiously ligand-independent fashion, to regulate MR expression, and hence MR-mediated acute and genomic effects. If corticosterone competes with aldosterone for GPR30 binding all is not lost, just as all is not lost for MR because it has equal affinity for both steroids. What has to be conjured with is under what circumstances aldosterone might regulate a significant minority of GPR30, and whether significant minority receptor occupancy is a sufficient basis for (patho)physiological effects.

If the first of those scenarios is the case, that GPR30 is truly an aldosterone-selective membrane receptor, mediating primarily acute aldosterone effects and possibly modulating genomic actions via its effects on MR transcription, we have a new dimension in mineralocorticoid action, and owe a debt of major thanks to Ross Feldman and his colleagues1 for what they have done. Presuming that the physiological response in a VSMC is constriction rather than apoptosis, it would serve to mediate the acute vasoconstrictor response to the rapid rise of aldosterone levels on postural change. The question of the physiological role of VSMC apoptosis at aldosterone levels of <10 pM would remain to be addressed, as would the potential roles of GPR30 in classical epithelial aldosterone target tissues and in nonepithelial tissues such as cardiomyocytes. There would be work to be done and pieces of the jigsaw to fit together, but the prospect is exciting, and the chance to substantially rewrite aldosterone (patho)physiology an enticing one.
But therapeutics are perhaps slightly fanciful until we know a considerable amount more about the distribution, range of tissue and organ actions, regulation of expression, and other facets of the physiology and pathophysiology of GPR30. What Gros et al\(^1\) have shown, for the first time, is that there is a validated membrane receptor which can be activated by aldosterone. This is a great point of departure; for this start, and the excitement it promises, we owe them a very sincere debt of thanks.

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**References**

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