Editorial Commentary

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

John W. Funder

See related article, pp 442–451

I

t is now generally accepted that in common with other steroid hormones aldosterone has rapid nongenomic effects, in addition to those mediated via DNA-directed, RNA-mediated protein synthesis. The currently accepted physiology of aldosterone was primarily charted by nephrologists, who understandably focused on the epithelial (and genomic) effects of aldosterone on urinary electrolytes, and the homeostatic changes in aldosterone secretion in response to sodium deficiency or potassium loading. The most acute physiological stimulus to aldosterone secretion, however, is assumption of the upright posture. Given this, it is not inappropriate to seek responses, similarly acute, to this rapid change in plasma aldosterone levels.

In the paper by Gros et al,1 the authors conclusively show that aldosterone at low picomolar concentrations can act rapidly via both GPR30 (originally an “orphan” G protein–coupled receptor, subsequently an erstwhile membrane estrogen receptor) and classic mineralocorticoid receptors (MR) over a range of parameters. These include extracellular signal-regulated kinase (ERK) 1/2 activation and myosin light chain phosphorylation in rat aortic vascular smooth muscle cells (VSMC) in vitro; for ERK activation, aldosterone has equivalent action via both receptors at low picomolar concentrations. The effects on GPR30 appear mineralocorticoid specific: in rat aortic endothelial cells, with MR expression below detection levels by Western blotting, aldosterone increased ERK activation with an EC₅₀ < 10 pM, an action abrogated by the GPR30 antagonist G15. In contrast, the effect of estradiol on inhibition of ERK activation was unaffected by G15 but blocked by the estrogen receptor α (ERα) antagonist ICI-182780.

The first point to be made is that these studies firmly establish GPR30 as a bona fide receptor for aldosterone, given the low picomolar concentrations used (except for myosin light chain phosphorylation, where inexplicably 10 nmol/L aldosterone was used, and Figures 8 and 9 point in quite different directions). Although GPR30 was also known as GPER, the latter designation was always on shaky ground: 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...
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 colleagues 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.

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 pathophysiological 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 in the Discussion but not 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 levering 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 a 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).
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 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.

**Sources of Funding**

None.

**Disclosures**

None.

**References**


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

John W. Funder

Hypertension. 2011;57:370-372; originally published online January 17, 2011;
doi: 10.1161/HYPERTENSIONAHA.110.165076

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
http://hyper.ahajournals.org/content/57/3/370

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published
in Hypertension can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial
Office. Once the online version of the published article for which permission is being requested is located,
click Request Permissions in the middle column of the Web page under Services. Further information about
this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Hypertension is online at:
http://hyper.ahajournals.org//subscriptions/