Mineralocorticoid and Epidermal Growth Factor Receptors
Partners In Vivo

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In the decade since the publication of the Randomized Aldactone Evaluation Study (RALES),[1] interest in the role of aldosterone and the mineralocorticoid receptor (MR) has increased exponentially. The comfortable notion that mineralocorticoid hypertension was just a matter of salt and water has been supplanted by a recognition that multiple tissues and systems are impacted.[2,3]

It is clear that the adverse cardiovascular consequences of mineralocorticoid-induced hypertension are far in excess of what might be expected for the magnitude and duration of the blood pressure rise.[4] These observations have focused research on the consequences of MR activation in nonepithelial tissues.[5] This represents somewhat of a renaissance as the consequences for the cardiovascular system of exposure to mineralocorticoids was first noted by Hans Seyle in 1946 and rediscovered by Brilla and Weber with further characterization by Young et al.[6] These investigators established a robust rodent model of mineralocorticoid-induced hypertension, cardiac hypertrophy, and cardiac fibrosis resulting from mineralocorticoid/salt administration over a period of weeks. The cardiac fibrosis is preceded by vascular inflammation and is independent of the hypertension, cardiac hypertrophy, angiotensin II, and potassium status. It is blocked by coadministration of MR antagonists (spironolactone or eplerenone) and, more importantly, once established, as in RALES, can be reversed by MR blockade.[6]

The response involves a number of tissues and/or cell types, including vascular endothelial cells, vascular smooth muscle cells, cardiomyocytes, fibroblasts, and inflammatory cells, particularly those of the monocyte/macrophage lineage. The identification of the relative contribution of each of these cell types, all of which, with the exception of the fibroblasts, contain the MR, is a critical first step in understanding the response. In *Hypertension* last year, tissue-specific deletion of MR was used to demonstrate a critical role for macrophage MR in the pathological response, although curiously this was without effect on the mononuclear cell infiltration per se.[7] Several lines of available evidence clearly demonstrate an important role also for endothelial cells in the response to aldosterone.[8] In this issue of the journal, Griol-Charhbili et al[9] describe their studies using an established mutant mouse to explore the role of the epidermal growth factor receptor (EGFR) in the vascular response to MR activation.

Why the EGFR? Grossmann and Gekle[10] have shown that aldosterone can induce rapid (5- to 10-minute) activation of extracellular signal-regulated kinase signaling through the EGFR. This response appears to involve MR, but not in a classic genomic pathway; the activation involves the cytosolic tyrosine kinase cSrc, which is known to activate EGFR.[10] Activation of the EGFR and its downstream effectors, such as extracellular signal-regulated kinase, is proliferative, and, indeed, the effects of angiotensin on extracellular signal-regulated kinase activity also involve the EGFR. Griol-Charhbili et al[9] seek to directly address the role of the EGFR in mediating mineralocorticoid/salt-induced vascular damage in vivo. The approach used is elegant in its simplicity. They take an "off-the-shelf" EGFR knockout mouse, the *waved-2* mouse from the Jackson Laboratories, and explore the response of the vasculature to treatment with aldosterone/salt for 4 weeks. The study focused extensively on the vasculature responses and, thus the consequences for inflammatory cell infiltration, cardiac fibrosis, and so forth, remain to be presented and/or explored. What was found, however, was unexpected. The lack of EGFR signaling did not alter vascular remodeling assessed by morphological criteria, elastin, and collagen densities. Lack of EGFR did, however, have consequences for vascular reactivity as measured by aortic relaxation in response to acetylcholine. This appears to be because of diminished levels of endothelial NO synthase in the vessel wall. It should be noted that, at baseline, markers of oxidative stress were increased in the vessel wall of the *waved-2* mice, but this did not translate into an altered structural response. One confounder may be that many studies, particularly those examining the coronary vasculature, use a longer period of mineralocorticoid/salt treatment, that is, 8 weeks.[6,7]

Although these results may be interpreted as evidence that the in vitro studies[10] have not recapitulated the in vivo situation, there are the usual caveats. In any germline knockout mouse, the possibility that there is redundancy and/or compensatory mechanisms (which may be recruited during development) must be considered. There are also temporal and spatial considerations. Many of the in vitro studies define responses over minutes rather than weeks. Griol-Charhbili et al[9] conclude that the role of the EGFR may be restricted to mediating the acute effects of MR activation, particularly those that occur through rapid nongenomic signaling, a proposition that is certainly consistent with existing data

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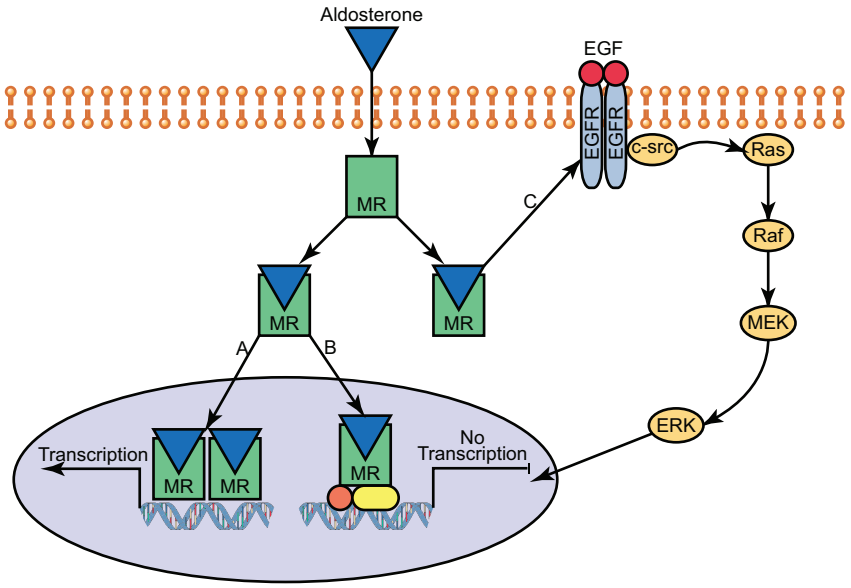

Figure. Schema demonstrating putative mechanisms involved in MR activation and signaling. A, The classic genomic pathway whereby aldosterone-bound MRs homodimerize and rapidly translocate to the nucleus where they bind specific hormone response elements (HRE) to initiate gene transcription. B, Transrepression by aldosterone-bound MR complexes, which interact with other transcription factors in an HRE-independent manner. C, Cytoplasmic second messenger signaling as a result of ligand-bound MR inducing rapid, nongenomic effects through activation of receptors, such as the EGFR.

(Figure). The relative contribution to the vascular response of the EGFR in the endothelium versus the EFGR in smooth muscle also remains to be determined.[9]

The question of "why the EGFR?" still hangs; it is only partially resolved. Although the roles of epidermal growth factor clearly extend beyond the dermis, the notion that EGFR serves only as an intermediate in a signaling cascade or in the integration of MR and angiotensin signaling in the vasculature seems improbable. What then is the ligand for the vascular EGFR? Where does it come from? Is it mediating growth or, perhaps, as in the epithelium of the gastrointestinal tract, repair? Yet, growth and/or repair would appear somewhat distant from issues of reactivity. Perhaps these questions are captive of the name? In biology, much of the nomenclature has a history akin to Christopher Columbus naming the islands of the "New World," the West Indies.

As with all good studies, the work of Griol-Charhbili et al[9] raises as many questions as it answers. What is indisputable is that the MR, which also arguably is misnamed, being rather more than just salt and water, plays a diverse role in cardiovascular physiology and pathophysiology.

Disclosures

None.

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