The simple assertion that aldosterone binds to the mineralocorticoid receptor (MR) and thereby promotes sodium reabsorption in the distal nephron should be largely revisited as it appears that this one ligand-one receptor-one action concept is no longer true. Several recent lines of evidence have now added a more complexified picture of the mechanisms and diversity of aldosterone action.

### 1. Endocrine and paracrine aldosterone

Aldosterone biosynthesis occurs mostly in the zona glomerulosa of the adrenal cortex and is the result of a series of complex enzymatic cascade. The first limiting step is the translocation of cholesterol into the inner mitochondrial membrane mediated by steroidogenic acute regulatory protein Star, followed by the side-chain cleavage enzyme, encoded by the CYP11A1 gene to produce pregnenolone. This latter is converted to progesterone by HSD3B2, followed by 21-hydroxylation (CYP21A) leading to deoxycorticosterone (DOC) production. The final and critical steps for aldosterone synthesis imply three consecutive reactions of 11β-hydroxylation, 18-hydroxylation and 18-methyloxidation, catalyzed by CYP11B1/B2 [1]. However, recently extra-adrenal synthesis of aldosterone, most notably in the central nervous system and in the cardiovascular system [2], has been proposed yet remained largely controversial questioning on the exact pathophysiological relevance of these findings.

### 2. Diversity of mineralocorticoid receptor action

Most aldosterone effects are mediated by the MR. MR is a classical ligand-dependent transcription factor, composed, as for the other nuclear receptors, of three distinct functional domains:

- the C-terminal ligand-binding domain (LBD) able to recruit specific coregulators to ensure coordinated control of target gene expression;
- the DNA binding domain representing the pivotal domain for functional interaction with hormone response elements;
- the N-terminal domain which now becomes a major determinant of MR action [3].

However, the functional interaction of MR with a large number of coregulators is more complex than expected and these interactions do not exclusively occur within the LBD [4]. MR may also act as a transcriptional factor without direct binding to DNA target sequences and may cooperate with other transcription factors to modulate specific gene transcription. Finally, among the steroid hormone receptors, MR is relatively unique as it is able to bind with almost the same affinity two distinct classes of hormones, the mineralocorticoids, aldosterone and DOC but also the glucocorticoids, cortisol and corticosterone in rodents. MR-mediated effects and their underlying molecular mechanisms are largely dependent on the cellular context. The 11β-hydroxysteroid dehydrogenase type 2 (11βHSD2) by catalyzing the metabolic conversion of active glucocorticoids into inactive 11 keto-derivatives ensures part of the specificity of aldosterone action in the classical sodium transporting epithelia [5,6]. Other specificity-conferring mechanisms are now identified including ligand-dependent MR interdomain interaction [7] and selective coregulator recruitment [8]. An additional degree of complexity now emerges as the MR gene does not encode one unique protein but rather gives rise to several mRNA isoforms and protein variants submitted to various posttranslational modifications [3], thus allowing combinatorial patterns of receptor expression potentially responsible for distinct cellular and physiological responses in a tissue-specific manner.
3. Genomic and non-genotropic effects of MR

Besides the classical genomic effects of aldosterone-MR [9], rapid aldosterone effects have recently been documented which seemed to be independent of transcription/translation [10]. Non genomic aldosterone signaling not only participates to the control of ionic homeostasis but also is involved in the pathogenesis of inflammation, cell proliferation and organ remodeling, most notably through a complex cross-talk with other signaling cascades including Angiotensin II [11] and epidermal growth factor receptor [12].

4. Kidney and beyond

The main and well-known effect of aldosterone via the MR in the distal segments of the nephron is the regulation of hydroelectrolytic balance by directly stimulating the expression and function of ionic transporters, including epithelial sodium channel and the sodium pump [3]. However, recently, it has been shown that aldosterone and MR also exert direct effects on glomeruli, especially mesangial cells [13] and podocytes [14], providing additional support for a pathophysiological impact of MR in proteinuric kidney diseases [15].

Besides the kidney, the central nervous system is another important MR-expressing target tissue [16,17], yet the absolute requirement of aldosterone for neuronal fate, survival and excitability, stress responses and behavioral adaptation may be not essential. The critical role of MR in the cardiovascular system is now well established owing to the beneficial effects of MR blockade (spironolactone, eplerenone) in reducing the morbidity and mortality of patients with cardiovascular disease [18,19]. However, cardiac fibrosis and pro-arrrhythmic effects are MR-mediated rather than aldosterone specific, even though hyperaldosteronism is clearly associated with increased incidence of cardiovascular dysfunction whose molecular mechanisms remained unclear. Aldosterone is also recognized as an important determinant of the vasculature pathophysiology, notably vascular function and structure. Hyperaldosteronism is linked to endothelial dysfunction and impaired vascular reactivity, possibly through a reduction of NO production and increased degradation via reactive oxygen species [20]. Aldosterone promotes proinflammatory vascular responses and increases proinflammatory mediators such as cytokines, growth factors and adhesion molecules.

Finally, in addition to the prominent role in controlling sodium and water balance and blood pressure regulation, MR and aldosterone also play pivotal roles in adipocyte biology. MR is a proadipogenic transcription factor in both brown [21] and white adipose tissues [22] and thereby likely participating to the pathophysiology of obesity and other metabolic disorders.

In conclusion, the impact of aldosterone-MR complex should not be restricted to the control of hydroelectrolytic homeostasis but rather extends to several pathophysiological processes such as central nervous system dysfunction, cardiovascular and renal remodeling and energy storage. In the context of this reevaluation of aldosterone physiology, the next challenge will be to get a better understanding on MR-mediated signaling both at the genomic and non-genotropic levels, for the design of new pharmacological strategies of modulating cell-specific MR action implicated in human diseases.

References