Comparison of Agents That Affect Aldosterone Action

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Summary: The first aldosterone blocker, spironolactone, initially was used as a diuretic but was accompanied by a significant amount of side effects that necessitated the withdrawal of the drug in a relevant number of patients. The discovery of the many receptor-mediated actions of aldosterone in several different organs greatly contributed to expand the indications of aldosterone blockers. Eplerenone was the second component of this class of drugs and differed from spironolactone because of its significantly better safety, albeit this was accompanied by a lower potency when used at equinumeric doses. Although these two drugs were being used in clinical practice, the epithelial sodium channel blockers, amiloride and triamterene, with a similar antialdosterone action, continued to be used in clinical practice in combination with thiazides and loop diuretics. New members of the third and fourth generation of mineralocorticoid receptor antagonists and aldosterone synthase inhibitors are in development. These new compounds, which include the new nonsteroidal mineralocorticoid-receptor antagonists and aldosterone synthase inhibitors, try to maintain adequate efficacy, avoiding the drawbacks of spironolactone and eplerenone. Ongoing studies will show the certainty of the capacities of these new compounds to override the virtues of the first mineralocorticoid-receptor spironolactone while avoiding the side effects leading so frequently to the withdrawal of the drug, including a significantly lower prevalence of hyperkalemia when chronic kidney disease is present.
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For many years, aldosterone was considered a hormone devoted to the control of renal excretion of minerals, which explains the term *mineralocorticoid* used to describe this hormone. Two clinical situations, primary and secondary hyperaldosteronism initially were considered for the clinical use of the first aldosterone-receptor blocker spironolactone as a diuretic. The discovery of many extrarenal sites of mineralocorticoid receptors[1,2] and the investigation of the proinflammatory and fibrogenic effects of the hormone[3] expanded the knowledge of the capacities of aldosterone to directly participate in the pathogenesis of arterial hypertension,[4] heart failure (HF),[5] chronic kidney disease (CKD),[6] and metabolic syndrome.[7] Eplerenone, the second most widely used blocker of aldosterone receptors, arrived when the role of these drugs as diuretics had been expanded to cardiorenal and metabolic disease. Data regarding canrenone, a third blocker of the receptor, are scanty. Finally, two other substances have been shown to antagonize the actions of aldosterone in the renal tubule, amiloride and triamterene, and they continue to be used as diuretics.

In this article, we review the role of aldosterone antagonists in aldosteronism, cardiorenal disease, and metabolic disease, and we refer in particular to the similarities and differences between the two main members of the class: spironolactone and eplerenone. Finally, we comment on the new members of the class, aldosterone antagonists, and their potential advantages.

EFFECTS OF ALDOSTERONE

Aldosterone, the final product of the renin-angiotensin-aldosterone system (RAAS), is a mineralocorticoid hormone secreted from the adrenal zona glomerulosa, which was isolated and characterized in 1953.[8] Until the mid-1990s, it was thought that aldosterone acts primarily in the epithelial cells of the late renal distal convoluted tubule and the collecting duct, distal colon, and salivary and sweat glands, leading to an increase in the net reabsorption of Na^+ and water and K^+ excretion. The reabsorption of Na^+ and water then increases blood pressure (BP) indirectly by expanding the extracellular fluid volume. These effects are mediated by the binding of aldosterone to mineralocorticoid receptors (MRs encoded by the NR3C2 gene), a ligand-dependent transcription factor belonging to the nuclear receptor superfamily.[8] However, after the molecular cloning of the MR in 1987, both experimental and clinical evidence showed that MRs are also

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present in a wide range of tissues, including endothelial and vascular smooth muscle cells, cardiac tissues (cardiomyocytes, fibroblasts, and macrophages), kidney (mesangial cells and podocytes), adipocytes, monocytes, and brain.[2,3,9]

Aldosterone produces genomic and non-genomic effects

Activation of MRs by aldosterone promotes multiple renal, cardiac, and vascular deleterious effects, including endothelial dysfunction, hypertension, neurohumoral activation, cardiovascular (CV) and renal remodeling (hypertrophy, fibrosis, and apoptosis), decreases arterial compliance, increases expression of cell adhesion molecules, platelet activation, plasminogen activator inhibitor type 1 (PAI-1) activity, and oxidative stress (by both nicotinamide adenine dinucleotide phosphate [NADP(H)], oxidase activity, and mitochondria), and exerts proarrhythmic and proinflammatory effects (Fig. 1).[1,3,5,10–12] In addition, activation of central MRs increases central sympathetic tone to the kidneys, heart, and vascular smooth muscles, increases vasopressin release, and decreases baroreceptor sensitivity. Moreover, aldosterone, via MR activation, up-regulates angiotensin-converting enzyme (ACE) expression in the cardiomyocytes, suggesting the existence of a positive feedback pathway that activates the renin-angiotensin-aldosterone system.[13] These effects are reported to be genomic (ie, dependent on transcription and translation).

In addition, aldosterone produces rapid, translation- and transcription-independent, effects (nongenomic effects) that may be mediated by G-protein–coupled receptor 30 and transactivation of the epithelial growth factor receptor.[3] These effects have been described in vascular smooth muscle cells (VSMCs) and other tissues in which aldosterone induces a rapid increase in Na^+ influx (aldosterone increases $Na^+/K^+/2Cl^-$ cotransporter activity and Na^+-H^+ exchange, and inhibits Na^+/K^+ adenosine triphosphatase [ATPase] activity) and intracellular Ca^{2+} concentrations through an increase in Ca^{2+} entry through voltage-gated channels, and activates cyclic adenosine monophosphate–protein kinase A, phospholipase C, phosphatidylinositol 3-kinase, diacylglycerol, and protein kinase C signaling pathways.[3,14,15] Aldosterone also induces a rapid phosphorylation of extracellular signal–regulated kinases 1 and 2 and c-Jun NH2-terminal kinase 1/2 kinase in VSMCs, endothelial cells, and kidney cells to promote a mitogenic and profibrotic phenotype, an effect that involves the transactivation of the epithelial growth factor receptor.[3,14,15] The nongenomic effects also occur independently of hemodynamic factors and play an important role in the mechanisms by which aldosterone contributes to endothelial dysfunction, vasoconstriction, resistant arterial hypertension, CV and renal remodeling, inflammation, heart failure, insulin resistance, and chronic renal disease (CKD).[1,3,5,7,14–18] Interestingly, in VSMCs, aldosterone activates both G-protein–coupled receptor 30 and MRs to mediate vasodilatation and apoptosis and to activate phosphatidylinositol 3-kinase, extracellular signal–regulated kinase, and myosin light chain phosphorylation.[15] In contrast endothelial MR activation has been linked to enhanced vasoconstrictor and/or impaired vasodilator responses.

The MR has the highest homology to the glucocorticoid receptor, and both receptors are expressed together in aldosterone target cells. In epithelial cells (kidney, endothelial cells, colon), aldosterone selectivity is determined by the 11-β-hydroxysteroid dehydrogenase 2 (11β-HSD2), an enzyme colocalized with the MR, which converts the active cortisol to the MR-inactive cortisone, but does not degradate aldosterone. However, other tissues (ie, cardiomyocytes, some regions of the brain) lack 11β-HSD2, so that cortisol is the primary ligand for the MR.[1] Thus, the tissue specificity of aldosterone is determined in part by the presence of 11β-HSD2. Although aldosterone and cortisol bind the MR with equal affinity, the aldosterone/MR complex is more stable, which in turn mediates a much stronger (200-fold) transactivation response than the cortisol/MR complex.[19] Whether the deleterious effects following MR activation are mediated by aldosterone and/or cortisol at conditions of inappropriate salt or redox status is a matter of discussion.[1]

All of these results confirm that aldosterone via MR-dependent and MR-independent mechanisms plays a pivotal role as a regulator of cellular and organ function, far beyond its effects on the kidney, and is involved directly in target organ damage in various CV and renal diseases.[3,11] This is the pharmacologic rationale for the development of aldosterone antagonists for the treatment of CV diseases (Table 1).

PHARMACOLOGIC MODULATION OF ALDOSTERONE

Mineralocorticoid-Receptor Antagonists

Three steroidal mineralocorticoid-receptor antagonists (MRAs) are presently on the market: spironolactone, eplerenone, and canrenoate (Table 1). Spironolactone and eplerenone have been widely studied in large randomized controlled trials (RCTs),[20–22] and potassium canrenoate (canrenone), an active metabolite of spironolactone, is available in some countries. Novel nonsteroidal compounds are presently in preclinical and early clinical development.

Spironolactone, the first MRA, was launched in 1960 as a K^+-sparing diuretic with a complementary mode of action to that of the diuretics currently used