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COMMENT

Inhibition of aldosterone synthase: Does this offer advantages compared with the blockade of mineralocorticoid receptors?

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The renin-angiotensin-aldosterone system (RAAS) is a key factor in the pathogenesis of hypertension and cardiovascular and renal diseases [1]. Given that angiotensin II, the main player of this system, induces vasoconstriction, vascular remodeling, and increases in aldosterone production via activation of the type 1 receptor, both angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) have been established to have beneficial clinical effects. However, the chronic inhibition of RAAS associated with the use of these agents can sometimes result in the failure of aldosterone suppression. This phenomenon, referred to as "aldosterone breakthrough", contributes to the development of resistant hypertension and progression of cardiovascular and renal diseases [2]. Moreover, ACE inhibitors and ARBs cannot inhibit the hypersecretion of aldosterone in primary aldosteronism, the most common cause of secondary hypertension. For these cases, antagonists of the mineralocorticoid receptor (MR), a major receptor for aldosterone, are recommended owing to their efficacy in controlling both blood pressure and disease progression [3]. Although traditional steroidal MR antagonists (spironolactone and eplerenone) have certain limitations with respect to their low selectivity and affinity for MR, respectively, novel highly selective and potent MR antagonists (esaxerenone and finerenone) have been developed for the treatment of hypertension and diabetic kidney disease [4].

An alternative approach to suppressing the activity of aldosterone involves the inhibition of aldosterone synthase (AS; CYP11B2). However, selectivity is the major issue regarding candidate AS inhibitors, as this enzyme has a high amino acid sequence similarity (95%) to that of cortisol synthase (CYP11B1) [5]. Osilodrostat, the first orally active AS inhibitor initially assessed for the treatment of primary aldosteronism and resistant hypertension [6], is now used for the treatment of hypercortisolism (Cushing's syndrome). In contrast, baxdrostat exhibited >100-fold selectivity for AS in vitro. In healthy subjects receiving single doses, baxdrostat dose-dependently reduced plasma aldosterone without affecting cortisol secretion [7]. Moreover, Freeman et al. reported that both the potent effects on plasma aldosterone and absence of effects on cortisol were sustained over 10 days in healthy subjects receiving multiple once-daily doses of baxdrostat [8]. Furthermore, in a phase 2 trial, patients with resistant hypertension, who received baxdrostat for 12 weeks, showed dose-dependent reductions in blood pressure with no serious adverse events or reductions in serum cortisol levels [9]. Based on these promising findings, it is thus anticipated that such new-generation AS inhibitors will gain acceptance as a viable option for the treatment of resistant hypertension and primary aldosteronism.

Given the aforementioned considerations, of the two drug classes (MR antagonists and AS inhibitors), which would be more effective? As shown in Fig. 1, MR is activated not only by aldosterone but also by cortisol and non-ligand stimuli (hyperglycemia, high salt, and oxidative stress) [4]. Consequently, the administration of AS inhibitors might only suppress a certain proportion of MR-mediated responses. Furthermore, in addition to its classical genomic effects mediated via MR as a transcription factor, aldosterone also has a range of rapid non-genomic effects [10]. These rapid effects of aldosterone may be mediated, at least in part, via alternative receptors, among which G protein-coupled estrogen receptor 1 is the most likely [11]. Theoretically, MR antagonists would not inhibit these MR-independent

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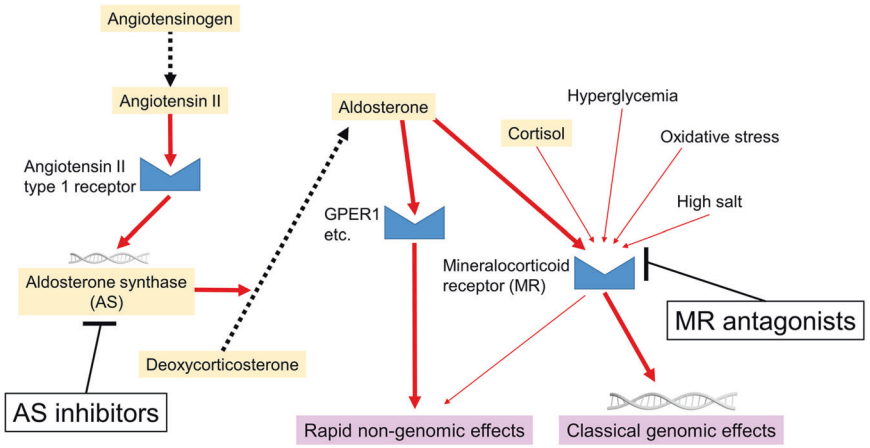

Fig. 1 The different mechanisms of action of mineralocorticoid receptor (MR) antagonists and aldosterone synthase (AS) inhibitors

effects. In addition, aldosterone plays beneficial roles in the central nervous system, colon, and kidneys, although detrimental effects in the cardiovascular system and kidneys are also evident [10]. Collectively, these considerations raise the possibility that MR antagonists and AS inhibitors differ in terms of clinical efficacy. We look forward to elucidating the relative merits and demerits of these two drug classes and, consequently, gaining further insights into the precise mechanisms underlying aldosterone-induced organ damage.

Compliance with ethical standards

Conflict of interest The author declares no competing interests.

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