Aldosterone synthase inhibitors in cardiovascular and renal diseases

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ABSTRACT

Aldosterone is involved in various cardiovascular pathologies, including hypertension, heart failure, atherosclerosis and fibrosis. Mineralocorticoid receptor (MR)-dependent and -independent, genomic and non-genomic processes mediate its complex effects. Spironolactone and eplerenone, both MR antagonists, are the only commercially available compounds targeting directly the actions of aldosterone. However, due to the poor selectivity (spironolactone), low potency (eplerenone) and the fact that only MR-dependent effects of aldosterone can be inhibited, these drugs have limited clinical use. An attractive approach to abolish potentially all of aldosterone-mediated pathologies is the inhibition of aldosterone synthase. This review summarizes current knowledge on the complex effects mediated by aldosterone, potential advantages and disadvantages of aldosterone inhibition and novel directions in the development of aldosterone synthase inhibitors.

Keywords: aldosterone synthase inhibitors, fibrosis, inflammation, mineralocorticoid receptor, oxidative stress

INTRODUCTION

The renin–angiotensin–aldosterone system (RAAS) is actively involved in various cardiovascular pathologies. Aldosterone, together with angiotensin II (Ang II), mediates oxidative stress, inflammation and tissue fibrosis. The underlying mechanisms are complex in their nature and involve mineralocorticoid receptor (MR)-dependent and -independent, genomic and non-genomic processes, and the interplay with Ang II, sodium and potassium. Moreover, the effects of aldosterone may vary in different tissues depending on aldosterone receptor distribution. Therefore, the pharmacological intervention targeting aldosterone pathway requires a broad knowledge about the mechanisms involved in aldosterone synthesis, molecular pathways involved in MR-dependent and -independent processes, discovery and description of putative aldosterone receptors and appropriate animal models of the human diseases. Here, the novel group of drugs, aldosterone synthase inhibitors (ASI), will be presented and their spectrum of action and side effects will be compared with MR antagonists.
Aldosterone synthesis

Aldosterone is synthesized from cholesterol mainly in the zona glomerulosa of the adrenal cortex. However, extra-adrenal sites of aldosterone synthesis have also been identified, including brain, vascular tissue and myocardium [1]. The enzyme aldosterone synthase, encoded by CYP11B2 gene, converts deoxycorticosterone to aldosterone in a series of enzymatic reactions. Another similar enzyme β-hydroxylase, encoded by the CYP11B1 gene, catalyses the conversion of deoxycortisol to cortisol. A high homology between β-hydroxylase and aldosterone synthase, ~95% at the amino acid level [2], implicates difficulties in the development of selective inhibitors targeting aldosterone synthesis.

Two main factors directly regulate aldosterone secretion—Ang II and potassium. Ang II is an effector peptide of the RAAS and acts on aldosterone secretion mainly via the angiotensin II type 1 receptor (AT1R), whereas the angiotensin II type 2 receptor (AT2R) counteracts many of the AT1R-mediated processes [3]. An increased level of potassium stimulates aldosterone leading to an increased renal potassium excretion. Under physiological conditions, both potassium and Ang II regulate aldosterone secretion equipotently and independently of each other [4].

Another potent aldosterone secretagogue factor is adrenocorticotropic hormone (ACTH). In an acute phase, ACTH induces aldosterone secretion; however, continuous ACTH stimulation has inhibitory effects [4]. Less potent secretagogue factors, including endothelin, vasopressin and serotonin, stimulate aldosterone secretion as well, but their exact physiological role remains unclear. In the modification of aldosterone synthesis, inhibitory factors, including somatostatin, atrial natriuretic peptides (ANP), dopamine and digoxin, are involved [3].

The understanding of aldosterone secretion requires differentiating between factors regulating the early and late pathways, the interplay between sodium, potassium and Ang II, the balance between secretagogue and inhibitory factors—all at the multiscale level. Therefore, further experimental approaches, including computational modelling and systems biology strategies, are needed.

MR-dependent and -independent effects of aldosterone

The effects mediated by aldosterone can be divided into MR-dependent and MR-independent. In both, genomic and non-genomic effects can be described (Figure 1).

In the most non-genomic, MR-dependent actions of aldosterone reactive oxygen species (ROS) serve as mediators. The aldosterone-induced ROS generation is associated with NADPH oxidase activation and can be inhibited by the selective MR antagonist eplerenone. Elevated ROS transactivate epidermal growth factor receptor (EGFR) leads to the activation of the Na⁺/H⁺ exchanger (NHE). Other ROS-dependent kinases, such as CaMKII or PKA, are also involved in aldosterone-mediated signalling [5].

The genomic, MR-dependent action of aldosterone can be further divided into hormone response elements (HREs)-dependent and -independent. Binding of MR to HREs in the promoter regions of EGFR gene, plasminogen activator inhibitor-1 (PAI-1), endothelin-1 and osteopontin activate transcription of their genes. Activated MR can also promote the nuclear translocation of calcineurin leading to the activation of nuclear factor of activated T-cells (NFAT). Another example of HRE-independent action of aldosterone is the association of MR with the transcription factor complex, P300/GATA4, resulting in an up-regulation of ANP [5].

Recently, several possible non-genomic MR-independent effects of aldosterone have been reported. It has been postulated that GPR30 (also known as G-protein-coupled oestrogen receptor, GPER) may act as an alternative aldosterone receptor and promote rapid, non-genomic effects in vascular endothelial cells [6] and vascular smooth muscle cells [7]. Gros et al. [7] have
shown that aldosterone activates intermediate signalling pathways including PI3 kinase, ERK and MLC phosphorylation leading to apoptosis, anti-proliferation and endothelium-dependent vasodilation. However, these findings require further investigation. Grossmann et al. [8] demonstrated an MR-independent, rapid effect of aldosterone leading to an increase in cytosolic Ca\(^{2+}\). However, the putative aldosterone receptor responsible for Ca\(^{2+}\) increase has not yet been identified.

Another non-genomic MR-independent effect of aldosterone is the increased elastin production in cardiac fibroblasts [9]. Binding of aldosterone to its putative receptor activates guanine nucleotide-binding protein \(\alpha_{13}\) (G\(\alpha_{13}\)) that interacts with cytosolic tyrosine kinase c-Src leading to activation of insulin-like growth factor-I receptor. In the presence of insulin-like growth factor-I, the transcription of elastin increases via the PI3K/Akt signalling pathway.

**PATHOLOGICAL EFFECTS OF ALDOSTERONE IN CARDIOVASCULAR SYSTEM**

Aldosterone exerts various and complex actions on cardiovascular tissues mediated by MR-dependent and -independent, genomic and non-genomic processes.

**Effects of aldosterone in the heart**

In patients with chronic atrial fibrillation (AF), an increased expression of atrial MR and elevated levels of aldosterone have been observed. The role of aldosterone in the pathogenesis of AF may involve atrial fibrosis, myocyte hypertrophy and conduction disturbances. Ionic remodelling can further induce the aldosterone/MR-mediated rhythm disorders. Modulation of T-type calcium channel expression, potassium and L-type calcium channel as well as ryanodine receptor activities lead to electrophysiological abnormalities observed in ventricular arrhythmias [10].

Aldosterone, mainly in association with sodium chloride load, induces expression of pro-inflammatory cytokines such as transforming growth factor \(\beta\) (TGF-\(\beta\)), adhesion molecules including ICAM-1 and VCAM-1 via MAPK and NF\(\kappa\)B as well as ROS in an MR-dependent and -independent manner. Moreover, Ang II further potentiates the aldosterone-mediated inflammation and oxidative stress. All of the deleterious actions of aldosterone may induce cardiac remodelling and fibrosis resulting in impaired cardiac function [10]. In patients with congestive heart failure (CHF), the aldosterone secretion rate is 4- to 5-fold higher than when compared with healthy subjects. The pharmacological blockade of MR reduces CHF-mediated oedema and improves cardiac function [1].

It should be mentioned that not every action of aldosterone in the cardiac tissue is deleterious. In 2009, Bunda et al. [9] showed that aldosterone stimulates the expression of the elastin gene in an MR-independent manner leading to an elevated production of elastic fibres by cardiac fibroblasts. This may, at least partially, counteract the MR-mediated maladaptive fibrosis in patients treated with MR antagonists. However, this issue needs more experimental evidence resulting in identification and description of the putative aldosterone receptor responsible for the elastogenic action.

**Effects of aldosterone in the vascular tissue**

Cachofeiro et al. [11] summarized the deleterious effects of aldosterone on vascular tissue in 2008. Therefore, only few important effects will be mentioned here. In addition, more recent research on the topic will be presented.

Aldosterone exerts multiple pathological actions on the endothelium including inflammation, oxidative stress, fibrosis and haemodynamic alterations that lead to increased barrier permeability, elevated vascular stiffness, endothelial dysfunction and may result in vascular remodelling. Numerous effects seem to be mediated by ROS, but other genomic MR-dependent and -independent effects contribute to harmful effects of aldosterone on vascular tissue as well.

Several studies focusing on haemodynamic alterations have provided different and contradictory conclusions, suggesting either vasoconstrictor or vasodilator action of aldosterone [11]. Recently, Gros et al. [6] postulated that the MR mediates vasoconstriction, whereas the GPER vasodilation. Thus, since the balance between GPER and MR expression vary across vascular beds, the effects of aldosterone are difficult to predict.

On the cellular level, aldosterone alters the assembly of adherens and tight junctions through the MR and via the RhoA/ROCK pathway, leading to increased endothelial permeability [12]. This mechanism may also be responsible for the reduced NO synthesis and, together with increased NO inactivation, may result in decreased NO availability.

The role of oxidative stress in endothelial dysfunction is well documented in various diseases. Aldosterone induces oxidative stress through multiple mechanisms, where both increased ROS synthesis and reduced ROS scavenging capacity are present in parallel [11]. This is mediated either directly via an MR-dependent mechanism or in crosstalk with the AT1R [13].

In a variety of cardiovascular diseases, aldosterone contributes to endothelial inflammation. The up-regulation of cytokines, chemokines and adhesion molecules followed by recruitment and adhesion of inflammatory cells is a common feature of aldosterone during initiation and progression of atherosclerotic lesion [11]. The activation of the NF\(\kappa\)B-pathway seems to play a crucial role in the pro-inflammatory actions of aldosterone.

Aldosterone is a well-known pro-fibrotic agent. Together with the pro-fibrotic activity of pro-inflammatory cytokines and elevated ROS production, aldosterone increases TGF-\(\beta\) and plasminogen activator inhibitor type 1 (PAI-1) expression, resulting in an increased synthesis of matrix proteins and decreased production of matrix metalloproteinases [13]. Aldosterone induces the expression of EGFR in an MR-dependent manner, leading to an elevated synthesis of fibronectin in aorta smooth muscle cells [14]. Recently, galectin-3 (Gal-3) has been suggested to be a key player in aldosterone-mediated fibrosis [15]. In rats, infusion of aldosterone elevated the expression of Gal-3 and pro-inflammatory cytokines accompanied by an increased deposition of collagen in aortic tissue. The pro-fibrotic effect of Gal-3 was abolished by an MR-antagonist and in Gal-3 knockout animals.

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**Effects of aldosterone in the kidney**

A number of studies investigating the role of aldosterone in kidney diseases demonstrated the importance of aldosterone in oxidative, inflammatory and fibrotic processes. The complex aldosterone-mediated effects in the kidney that imply genomic and non-genomic mechanisms have been extensively described elsewhere [16] and so will only be mentioned briefly here.

Several clinical studies revealed that the incidence of proteinuria and albuminuria is higher among patients with primary aldosteronism when compared with those with essential hypertension [16]. Moreover, in populations with primary aldosteronism, chronic kidney disease or diabetic nephropathy, plasma aldosterone levels positively correlated with urinary protein excretion levels and negatively with glomerular filtration rate. These findings are supported by a number of animal studies where the impact of aldosterone on renal injury via oxidative stress, inflammation, fibrosis and haemodynamic alterations was shown.

The pro-inflammatory action of aldosterone in the kidney is mediated via the NFκB pathway and contributes to glomerulosclerosis and tubulointerstitial fibrosis [16]. Aldosterone in an MR-dependent manner induces phosphorylation of serum/glucocorticoid regulated kinase 1 (SGK1) that activates NFκB, resulting in elevated synthesis of cytokines, chemokines, adhesion molecules and growth factors. Another factor that contributes to renal injury is oxidative stress. As previously mentioned, aldosterone induces ROS production via MR-dependent mechanisms. The blockade of ROS synthesis by tempol prevents the progression of proteinuria and renal injury. These findings are supported by a number of animal studies where the impact of aldosterone on renal injury via oxidative stress, inflammation, fibrosis and haemodynamic alterations was shown.

Both, inflammation and oxidative stress, contribute to the fibrotic changes; however, aldosterone can also directly induce the expression pro-fibrotic molecules. Aldosterone stimulates the expression of PAI-1 in SMC, leading to the elevated levels of TGF-β. This, in turn, promotes fibroblast differentiation, proliferation and fibrosis [17]. In addition, at high concentrations, aldosterone is able to stimulate glucocorticoid receptors, leading to up-regulation of profibrotic connective tissue growth factor (CTGF) [18].

**MR Antagonists**

MR antagonists can be divided into steroidal, including spironolactone and eplerenone, and non-steroidal compounds (heterogeneous group with novel compounds in development). The molecular pharmacology of these compounds was summarized by Kolkhof and Borden [19].

The first MR antagonist, spironolactone, was marketed in 1960 for the management of oedematous conditions, primary aldosteronism and essential hypertension. It is a potent MR antagonist, albeit with poor selectivity for the MR. Several adverse effects have been reported for spironolactone, which reflects its significant anti-androgenic and progestagenic activity.

In 2002, a novel MR antagonist, eplerenone, was launched for the treatment of CHF. When compared with spironolactone, eplerenone has an improved selectivity for MR, but it features a reduced potency (40-fold lower affinity for MR when compared with spironolactone).

Pfizer developed the first non-steroidal pyrazoline MR antagonist, PF-3882845, with greater potency and selectivity when compared with steroidal compounds. Yet, after Phase I studies, it was discontinued from development in August 2012.

In 2004, it was shown for the first time that dihydropropiridines (DHP) compounds, known as established L-type calcium channel antagonists, can also act as MR antagonists. The optimization programmes led to the development of a selective and potent DHP-based MR antagonist, BR-4628, without significant activity at the L-type calcium channel. In contrast to eplerenone, DHP-based L-type calcium channel antagonists inhibit nuclear translocation of MR.

Recently, based on DHP compound structures, a novel dihydroanaphthyridine class of non-steroidal MR antagonists has been developed. The lead compound, BAY 94-8862, has a much higher selectivity for the MR, an improved PK profile and natriuretic effects when compared with eplerenone. It is currently investigated in a clinical Phase II trial in chronic heart failure patients with renal impairment.

**Pharmacology of ASI**

The first orally active compound targeting aldosterone synthase was FAD 286. In the late 1980s, it was shown that flazo, an aromatase inhibitor used for the treatment of hormone-dependent breast cancer, induced an increase in the blood 18-hydroxy corticosterone/aldosterone ratio, suggesting aldosterone synthase inhibition. A decade later, the study on its enantiomers led to the isolation of a dextrorotatory enantiomer (FAD 286) with higher potency and selectivity for aldosterone synthase. FAD 286 inhibits human recombinant aldosterone synthase (CYP11B2) in vitro with an IC₅₀ of 1.6 nM, and β-hydroxylase (CYP11B1) with an IC₅₀ of 9.9 nM, indicating poor selectivity (selectivity ratio ≈6). In an animal model of hyperaldosteronism, FAD 286 showed a 50-fold selectivity for reducing plasma aldosterone concentration (PAC) versus plasma corticosterone concentration (PCC) [20].

Based on the FAD286 structure, a new ASI, LCI699, has been developed for human use in 2010 [21, 22]. So far, in vitro data on receptor selectivity and specificity for LCI699 have only been disclosed in one patent application [23]. A comparison of multiple drugs revealed that LCI699 inhibits CYP11B2 at an IC₅₀ of 7.6 nM and CYP11B1 at an IC₅₀ of 35 nM, giving a selectivity ratio of 4.6 [23]. In healthy males, LCI699 is absorbed within 1 h and has a plasma half-life of 4 h. Multiple oral doses decreased plasma and urine aldosterone concentration by up to 70%. LCI699 selectively inhibited aldosterone synthesis at a dose of 0.5 mg q.d.; however, at doses ≥1 mg o.d., its selectivity was lost. At 3 mg, signs of a mild hypoaldosteronism were observed [21, 22].

An interesting novel group of pyrazole derivatives that act as potent and selective ASI have recently been described [24]. Two promising compounds, No. 1 and No. 49, inhibit the CYP11B2 at an IC₅₀ of 5 and 7 nM, and the CYP11B1 at the...
full review

**ANIMAL STUDIES WITH ASI**

In spontaneously hypertensive rats on a low sodium/high potassium diet, FAD286 decreased plasma and urine aldosterone concentration and increased plasma renin activity [27]. In contrast to eplerenone, treatment with FAD286 did not reduce systolic blood pressure (BP) in high salt diet-fed uninephrectomized rats. However, both agents normalized elevated urinary protein levels [28]. Interestingly, cerebroventricular infusion of FAD286 reduced BP, sympathetic hyperactivity and baroreflex impairment in rats centrally infused with hypertonic saline [29].

Most of the animal studies with ASI focus on the protection against end-organ damage. In an animal model overexpressing human renin and angiotensinogen genes (dTRG rats), treatment with FAD286 reduced mortality, cardiac hypertrophy, cell infiltration and matrix deposition in heart tissue [30]. This was accompanied only by a slight decrease in BP at Week 7 of treatment. A study performed by Mulder et al. [31] compared the impact of ASI with MR antagonists in an animal model of CHF. Both agents, FAD286 and spironolactone, decreased left ventricular hypertrophy and collagen accumulation to the same extent, but FAD286 reduced left ventricular end-diastolic pressure and left ventricular dilatation more than spironolactone. Interestingly, only FAD286 reduced CHF-related oxidative stress and abolished the reduction of AT2R expression in the left ventricle. Since the AT2R plays an important cardioprotective role [32], restored expression of the ‘protective arm of RAAS’ may have contributed to the beneficial effects observed in FAD286-treated animals.

Several studies investigated the aldosterone synthase inhibition in renal protection. In the above-mentioned study by Fiebeler et al. [30], dTRG animals treated with FAD286 were characterized by reduced albuminuria, significantly lowered monocyte and macrophage infiltration as well as reduced collagen deposition. Another end-organ damage model, high salt diet-fed uninephrectomized rats chronically infused with Ang II, displayed pronounced kidney injury characterized by fibrotic processes and renal vascular remodelling [33]. Treatment with FAD286 or spironolactone reduced albuminuria, renovascular hypertrophy, glomerular injury as well as tubulointerstitial fibrosis in the kidney. Interestingly, spironolactone treatment transiently increased circulating PAI-1, whereas FAD286 had no effect.

The impact of aldosterone synthase inhibition on the development of atherosclerosis was studied in apolipoprotein E-deficient mice [34]. Animals fed with a low-salt diet exhibited increased atherosclerotic lesion areas in the aorta, accompanied by elevated serum and urine aldosterone levels. Treatment with FAD286 reduced atherosclerosis and inflammation markers in isolated macrophages without any effect on total serum cholesterol, high-density lipoprotein or triglyceride levels. Surprisingly, FAD286-treated animals showed similar serum aldosterone levels and slightly elevated urine aldosterone levels when compared with the low-salt diet animals. This is in contradiction to previously published data and should be analysed carefully in the future.

An interesting and novel therapeutic indication for ASI is retinopathy. The neovascularization, a maladaptive growth of blood vessels leading to haemorrhage and consequently to blindness, is mediated by VEGF and largely controlled by the RAAS. In an animal model of the oxygen-induced retinopathy (OIR), the impact of FAD286 on the neovascularization was studied in comparison with the AT1R blocker valsartan [35]. Both drugs strongly reduced neovascularization and neovascular tufts in OIR, accompanied by the reduced microglial infiltration. The underlying mechanisms involve reduced levels of VEGF, TNF-α, MCP-1, ICAM-1 and VCAM-1. Interestingly, the combination of FAD286 and valsartan had no additive effect and, for some parameters, even tended to act in a subtractive manner.

For the study of pharmacological intervention in hyperaldosteronism, several strategies can be used, including low-sodium diet, potassium supplementation and diuretic/natriuretic treatment. Unfortunately, these models are characterized by a high variation of elevated PAC and often provide contradictory results. In 2010, Rigel et al. [20] established two models of hyperaldosteronism. Chronic infusion of Ang II or adrenocorticotropin resulted in a stable elevated PAC, whereas an increase in PCC was observed only in adrenocorticotropic-infused animals. Treatment with FAD286 or with metyrapone, an 11 β-hydroxylase inhibitor, both reduced elevated PAC; however, FAD286 was 12 times more dose-potent than metyrapone. Moreover, FAD286 was 50-fold selective for reducing PAC versus PCC, whereas metyrapone was only 3-fold selective.

**CLINICAL STUDIES WITH ASI**

The only ASI used in humans so far is LCI699. In Phase II studies, the impact of LCI699 on hypertension and hyperaldosteronism was investigated.

A group of 524 patients with primary hypertension (Stage 1–2 hypertension) was randomized between six treatment groups: LCI699 0.25, 0.5 or 1.0 mg q.d., LCI699 0.5 mg b.i.d., eplerenone 50 mg b.i.d. or placebo for 8 weeks [36]. All doses of LCI699 significantly reduced 24-h ambulatory BP when compared with placebo. Only 1.0 mg of LCI699 significantly decreased office diastolic BP (−7.1 mmHg) comparably to eplerenone treatment (−7.9 mmHg). The ACTH stimulation...
of cortisol was suppressed in 20% of LCI699-treated patients; however, no signs of hypocortisolism were observed.

In a small proof-of-concept study, 14 patients with primary aldosteronism received sequentially LCI699 at the doses 0.5 mg b.i.d. and 1.0 b.i.d. each for 2 weeks, followed by placebo for 1 week [37]. After 4 weeks of LCI699 treatment, a slight decrease in 24-h systolic BP was observed (−4.1 mmHg). As expected, LCI699 induced dose-dependent decrease in plasma and urinary aldosterone concentrations by up to 80%. Unfortunately, all 14 patients displayed fully blunted cortisol responses to ACTH after 4 weeks of treatment, implicating poor selectivity of LCI699 for aldosterone synthesis.

In the follow-up study, 14 patients with primary aldosteronism treated in a sequential manner with LCI699, as described above, were switched to standard treatment with eplerenone (50 mg b.i.d. up-titrated to 100 mg b.i.d. in 12 patients) for 30 days [38]. LCI699 decreased PAC by 75%, whereas eplerenone increased it by 89%. Treatment with eplerenone decreased 24-h ambulatory systolic BP and increased plasma potassium and plasma renin concentrations more efficiently when compared with LCI699 treatment.

The selectivity of the LCI699 with respect to the suppression of cortisol levels was studied in 63 patients with essential hypertension [39]. Patients were treated with various doses of LCI699, and the ACTH-stimulated cortisol response was evaluated. The study confirmed the limited selectivity of aldosterone synthase inhibition and estimated themaximally tolerated dose to be 1.3 mg q.d. Treatment with the two highest doses of LCI699 had a statistically significant effect on the mean seated systolic BP (−12.5 mmHg for 1.0 mg of LCI699 b.i.d. and −10.9 mmHg for 2.0 mg of LCI699 q.d. when compared with placebo). Similarly, 1.0 mg of LCI699 q.d. and 1.0 mg of LCI699 b.i.d. significantly reduced the mean seated diastolic BP when compared with placebo (−9.1 and −9.2 mmHg, respectively).

The antihypertensive effect of LCI699 was further studied in patients with resistant hypertension [40]. A population of 155 patients was randomized to five treatment groups: LCI699 0.5 mg b.i.d. up-titrated after 4 weeks to the 1.0 mg b.i.d., LCI699 0.25 mg b.i.d., LCI699 1.0 mg q.d., eplerenone 50 mg b.i.d. and placebo, for 8 weeks. Treatment with eplerenone significantly reduced systolic and diastolic BP (in relation to placebo −9.9 and −2.9 mmHg, respectively), whereas LCI699 had a smaller, non-significant effect on BP reduction. The reason for the lack of BP-lowering effect in patients with resistant hypertension compared with essential hypertension remains unclear.

Currently, the efficacy and safety of LCI699 is studied in patients with Cushing’s disease. Estimated completion of the study is the end of 2014.

CONFLICT OF INTEREST STATEMENT
None declared.

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PERSPECTIVE

Our current knowledge of the in vivo beneficial action of ASI is limited due to the poor selectivity of the tested compounds. FAD286 tested in animal studies and LCI699 tested in humans showed some tissue protection; however, both drugs exhibit clear side effects due to the inhibition of CYP11B1. Therefore, the novel selective ASI that are presented here should be tested for the efficacy and safety in animal models.

The above-cited clinical studies make it difficult to believe that ASI will become first-choice drugs for the treatment of hypertension. However, it would be interesting to study the impact of ASI in combination with MR antagonists or AT1R blockers on BP reduction in patients with resistant hypertension or low renin/high aldosterone hypertension. Further potential indications for ASI are CHF, chronic kidney disease and primary aldosteronism.

The advantages and disadvantages of aldosterone synthase inhibition should be discussed in comparison with the MR antagonists. The theoretical advantage of ASI is the reduction in circulating and local aldosterone with its potentially harmful effects by an MR-independent manner. However, this topic needs further research—the MR-independent effects of aldosterone should be better characterized and the putative receptors for aldosterone identified. On the other hand, treatment with ASI may allow the activation of the unprotected MRs by glucocorticoids [41]. Both drug classes may cause hyperkalemia, hyponatremia as well as renal insufficiency, and this issue needs further consideration.


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