Current Hypertension Reports (2019) 21: 23
https://doi.org/10.1007/s11906-019-0923-1

ANTIHYPERTENSIVE AGENTS: MECHANISMS OF DRUG ACTION (MICHAEL E. ERNST, SECTION EDITOR)

Emerging Therapy in Hypertension

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Published online: 2 March 2019

Abstract

Purpose of the Review Pharmacology remains the mainstay of treatment for hypertension across the globe. In what may seem like a well-trodden field, there are actually an exciting array of new pathways for the treatment of hypertension on the horizon. This review seeks to discuss the most recent research in ongoing areas of drug development in the field of hypertension.

Recent Findings Novel areas of research in the field of hypertension pharmacology include central nervous system regulators, peripheral noradrenergic inhibitors, gastrointestinal sodium modulators, and a counter-regulatory arm of the renin-angiotensin-aldosterone system.

Summary This review discusses these pathways in a look into the current status of emerging pharmacological therapies for hypertension.

Keywords Hypertension · Future hypertension therapy · Hypertension drugs · Pharmacological therapy · High blood pressure · Hypertension medication

Abbreviations

ACE	Angiotensin-converting enzyme
ACTH	Adrenocorticotropic hormone
Ang	Angiotensin
Ang I	Angiotensin I
Ang II	Angiotensin II
Ang III	Angiotensin III
AngA	Angiotensin A
ANP	Atrial natriuretic peptide
APA	Aminopeptidase A
ARB	Angiotensin receptor blocker
ASI	Aldosterone synthesis inhibitors
AT1	Angiotensin receptor 1
AT2	Angiotensin receptor 2
BNP	Brain natriuretic peptide
C21	Compound 21
CNS	Central nervous system
DBH	Dopamine-beta-hydroxylase
DIZE	Diminazene aceturate
MrgD	Mas-related G protein–coupled receptor D
NHE3	Sodium/hydrogen exchanger 3
NO	Nitric oxide
RAAS	Renin-angiotensin aldosterone system
SBP	Systolic blood pressure

This article is part of the Topical Collection on *Antihypertensive Agents: Mechanisms of Drug Action*

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Introduction

Of the 1.39 billion people worldwide who currently have hypertension, only 36% are on treatment and only 14% are under control with a systolic blood pressure < 140 mmHg [1]. This is despite a dramatic growth in hypertension pharmacotherapy over the past 50 years, starting with thiazide diuretics in the 1950s to a now expansive list of at least eight major commercially available categories. The reasons for inadequate control are many and include resistant hypertension requiring three or more medications or medication intolerance. To this end, the continued development of more effective and better tolerated anti-hypertensive treatment is an ongoing area of research.

Within the past 3 years, current anti-hypertensive medication development has been in one of several areas. These

include alternative pathways in renin-angiotensin aldosterone system (RAAS), central RAAS mechanisms, novel mineralocorticoid receptor antagonists, renin inhibitors, aldosterone synthesis inhibitors, sympathetic neurotransmitter blockade, and gastrointestinal sodium reduction (Table 1).

The Angiotensin-Converting Enzyme 2/Angiotensin (1–7)/Angiotensin Receptor 2/Mas Receptor Axis

The traditional components of the RAAS system are well known and include angiotensin I (Ang I), angiotensin-converting enzyme (ACE) 1, angiotensin II (Ang II), and angiotensin receptor 1 (AT1). The system though is in fact much more complex that this three-protein paradigm originally described. There exists an alternative counter-regulatory pathway with components including angiotensin (Ang) (1–7), peptide Alamandine, enzyme ACE 2, angiotensin receptor 2 (AT2), Mas receptor, and Mas-related G protein–coupled receptor D (MrgD). ACE 2 converts Ang II from the classical pathway to Ang (1–7) in the alternative pathway, which goes on to interact with the AT2 and Mas receptors. ACE 2 also converts Angiotensin A (AngA), a product of angiotensin II, into Alamandine, which interacts with the MrgD receptor [2]. With the multitude of peptides and receptors, it is important to understand that there is continuous cross-talk and often one peptide will have some degree of affinity for multiple competing receptors [3] (Fig. 1).

The AT2 receptor is found in many of the same tissues as the AT1 receptor, such as the kidney, heart, vasculature, brain, and adrenal gland [4]. Activation of the AT2 receptor has been shown to result in vasodilation, diuresis, natriuresis, and also non-cardiovascular anti-fibrotic, anti-thrombotic, and anti-proliferative effects [5]. The Mas receptor has similar effects as the AT2 receptor, promoting vasodilation, and co-localizes with the AT2 receptor [6]. Once triggered by any particular ligand, the sub-membrane interdependence between these G-coupled receptors (AT2, AT1, Mas, and MrgD) continues to remain an active area of research [6]. Within the alternative RAAS pathway, pharmacological strategies for hypertension management include increasing ACE2 activity, replicating Ang (1–7), and stimulating the AT2 or MrgD receptors (Fig. 1).

ACE2

Diminazene aceturate (DIZE) is a veterinary anti-trypanosomal medication first used in the 1950s, but has gained renewed interest in the past 10 years as it has been found to activate the ACE2 enzyme [7]. It remains in the preclinical phase, but recent studies have shown that DIZE causes a dose dependent significant reduction in blood pressure in both normotensive and hypertensive rats [8]. The anti-hypertensive effects of DIZE are predominantly vasodilatory, as isolated renal infusions of DIZE do not result in blood pressure lowering [9]. This is also suggested by the rapid onset of action in the setting of intravenous preparations [8]. In addition to vasodilation, DIZE also has beneficial effects

Table 1 Emerging therapy in HTN

Drug	Mechanism of action	HTN trial stage	Most recent HTN publication
DIZE[10]	ACE2 activator	Preclinical	2016
Recombinant ACE 2[13,14]	ACE2	Phase II	2013
AVE0991[24]	AT2/Mas receptor agonist	Preclinical	2017
Almandine[29]	MrgD receptor agonist	Preclinical	2018
C21[39]	AT2 receptor agonist	Preclinical	2018
LCI699[46]	Aldosterone synthase inhibitor	Phase II	2013
BI 689648[47]	Aldosterone synthase inhibitor	Preclinical	2016
LY3045697[48]	Aldosterone synthase inhibitor	Phase I	2017
RO6836191[49]	Aldosterone synthase inhibitor	Phase I	2017
Finerenone[51]	Mineralocorticoid antagonist	Phase III	2016
LCZ696[59,60]	Neprilysin inhibitor/ARB	Approved (off-label)	2017
Etamicastat[64]	DBH inhibitor	Phase I	2015
Zamicastat[65,66]	DBH inhibitor	Phase I	2018
Aliskiren[72]	Direct renin inhibitor	Approved	2018
Tenapanor[76]	NHE3 inhibitor	Phase III	2018
SAR[77]	NHE3 inhibitor	Preclinical	2016
RB150/QGC001[82,83]	Aminopeptidase A inhibitor	Phase II	2018

ACE2, angiotensin-converting enzyme 2; *ARB*, angiotensin receptor blocker; *AT2*, angiotensin receptor 2; *NHE*, Na+/H+ exchanger; *DBH*, dopamine-beta-hydroxylase

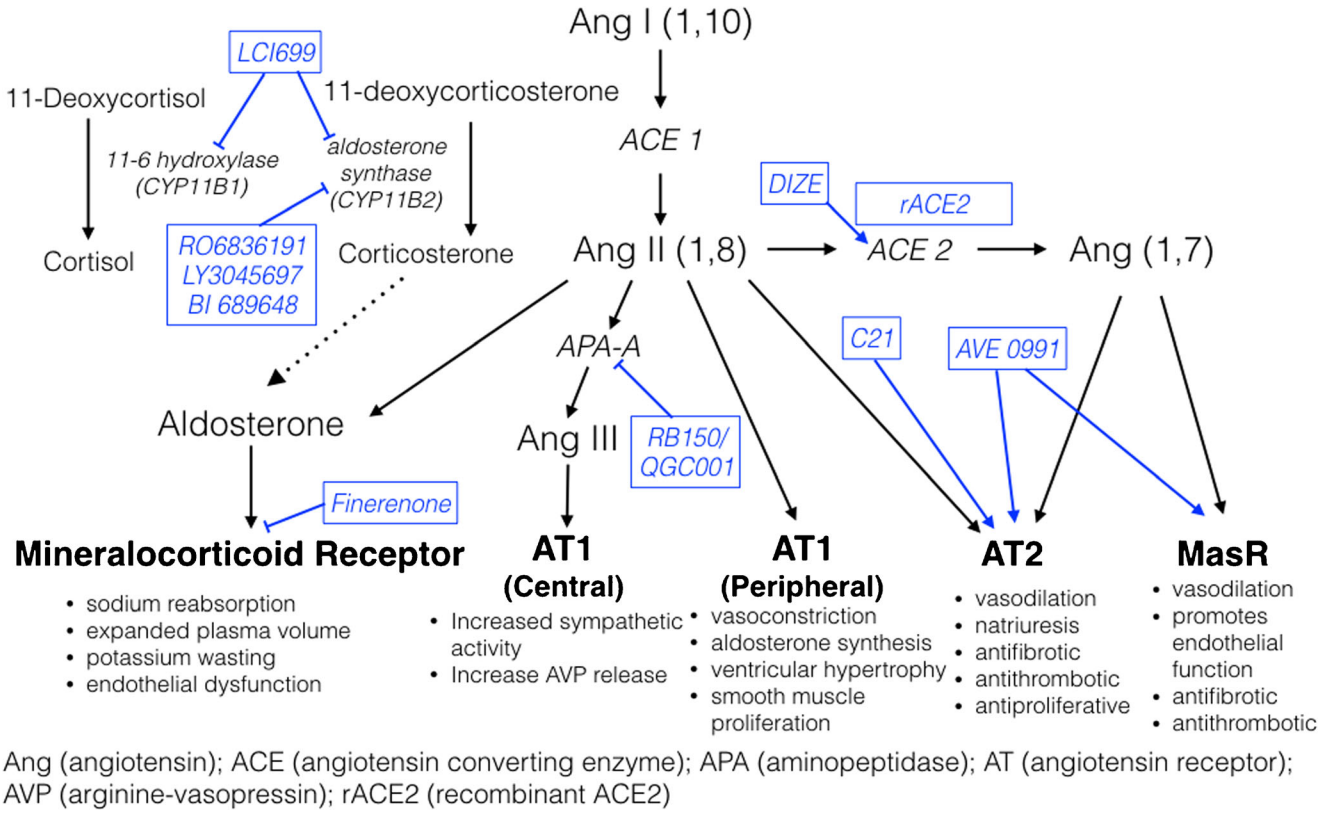

Fig. 1 Emerging pharmacology in the RAAS system

similar to ACE inhibitors, preventing the onset of left ventricular hypertrophy in aortic banded rats [10]. Unfortunately, DIZE is not currently available for humans due to documented side effects such as a tremors and convulsions in animals [11]. With more understanding of the mechanism of activation, a similar focused pharmaceutical may be developed.

Other recent techniques for ACE2 activation include gene therapy and recombinant ACE2. Gene therapy has been shown to successfully prevent hypertension-related aortic aneurysms in mice, but it is still in preclinical testing [12]. Recombinant ACE2 has been studied in a phase I trial in humans and safely reduces levels of Ang II while increasing levels of Ang (1–7) [13]. This initial trial showed no immediate hemodynamic effects, but larger phase II trials are ongoing [14].

Angiotensin (1–7)

Ang (1–7) sits as the central peptide within to the counter-regulatory RAAS pathway. It has affinity for the AT1, AT2, and Mas receptors but preferentially activates the AT2 and Mas receptors while simultaneously competing with Ang II for binding sites on the AT1 receptor, thereby attenuating its effects [15]. Infusion of Ang (1–7) in animals results in blood pressure reduction, decreased ventricular hypertrophy, and improved renal function [16, 17]. Despite the awareness of potential benefits, Ang (1–7) has not been studied in humans as thoroughly given, it is a peptide with a short half-life requiring continuous intravenous infusion [4]. Nonetheless, there are several currently enrolling phase I trials looking at the effects of intravenous and subcutaneous Ang (1–7), the results of which have not been published as of this writing [18, 19].

As an alternative to intravenous Ang (1–7), biologically stable non-peptide alternatives have been developed including AVE0991. AVE0991 was first described over 15 years ago, having properties similar to Ang (1–7) with agonist effect on the Mas and AT2 receptors [20]. Orally administered, AVE0991 has been shown in animals to cause vasodilation and decrease post infarction vasoconstriction [21]. The effects of AVE0991 on the AT2 and Mas receptors are mediated in part by bradykinin and nitric oxide (NO). AVE0991 is also capable of restoring endothelial dysfunction due to high-salt diets [22]. AVE0991 attenuates the effects of aortic banding on cardiac hypertrophy in mice and reduces oxidative stress [23]. In addition to anti-hypertensive properties, AVE0991 also reduces inflammation and atherosclerosis in hyperlipidemic mice. AVE0991 has not yet been studied in humans and is still in preclinical research [24].

Alamandine

Alamandine is a vasoactive peptide discovered in 2013 and is the derivative of AngA being converted by the enzyme ACE2. Alamandine selectively acts on the MrgD receptor which is

similar to the Mas receptor, promoting vasodilation and antiproliferation [2]. Alamandine is morphologically similar to Ang (1–7), and the comparative difference between the Almandine-MrgD and Ang (1–7)-Mas receptor axes is still under investigation [25]. MrgD receptors are also found in the central nervous system, suggesting a central in addition to peripheral mechanism of action. Indeed injection of Alamandine into the medulla of hypertensive rats results in sustained hypotension [26]. Alamandine is similar to AVE0991 in that it results in decreased ventricular hypertrophy in animal models of hypertension [27]. Peripherally administered Almandine also results in blood pressure reduction and decreased reperfusion injury after ischemia [28, 29]. Similar to Ang (1–7), it is a peptide and must be administered as an infusion or subcutaneous injection, which is one of the reasons it has not yet been studied in humans.

AT2 Receptor Agonism

The AT2 receptor was the first studied receptor in the counter-regulatory RAS pathway and has been described as a subtype of the angiotensin receptor for 30 years [30]. Mice with AT2 receptor overexpression exhibit a lower blood pressure than controls, and AT2 knockout mice have a significantly higher blood pressure [31, 32]. Stimulation of AT2 results NO and bradykinin-mediated vasodilation [33]. There has been some difficulty studying AT2 as a mechanism for blood pressure control given that it is only expressed at fraction (5–10%) of the rate as the AT1 receptor, and it shares many of the same ligands as AT1, most importantly Ang II [34]. The first selective ligand of AT2 receptor was a peptide labeled CGP-42112A, but faced much of the same difficulty as the peptide Ang (1–7) including a short half-life and requirement for intravenous infusion [35]. More recently, a non-peptide AT2 receptor agonist, Compound 21 (C21), was developed in 2004 in Sweden with a 4-h half-life and 30% oral bioavailability [36]. Early studies with this medication showed that a concomitant administration of an ARB for AT1 receptor inhibition was required to achieve a response due to the interdependent nature of these receptors [37]. As such, it was not developed rapidly into an independent class of medication, but C21 continues to be studied actively to find its beneficial niche. Recent trials in rats have shown that C21 induces natriuresis and decreases blood pressure in an Ang II infusion model of hypertension [38]. In hypertensive-related diseases, C21 prevents the progression of a murine model of abdominal aortic aneurysm, attenuates the progression of diabetic-related atherosclerosis, and prevents myocardial hypertrophy [39–41].

Aldosterone

Mineralocorticoid antagonism was first studied in the 1950s with spironolactone, however, remained a second line agent due to anti-androgenic effects and effective alternative agents [42]. Recently after the PATHWAY-2 trial demonstrated greater efficacy of spironolactone over bisoprolol and doxazosin in resistant hypertension, mineralocorticoid antagonism has taken on renewed interest [43].

Aldosterone Synthesis Inhibitors

A novel approach to this pathway was the development of aldosterone synthesis inhibitors (ASI) which work upstream of aldosterone production to inhibit the conversion of 11-deoxycorticosterone to corticosterone by blocking the enzyme CYP11B2. The first drug in this class was LCI699 which showed promise in early phase I and phase II trials [44, 45]. Ultimately, though LCI699 was proven inferior to other commonly used mineralocorticoid antagonists due to the homology between CYP11B2 and CYP11B1, an enzyme in the cortisol synthesis pathway [46]. Concomitant inhibition of cortisol synthase/CYP11B1 resulted in increased adrenocorticotropic hormone (ACTH), which drove the production of other vasoactive peptides negating the effect of CYP11B2 inhibition. As the result of these findings, several new specific ASI/CYP11B2 inhibitors have been developed in the past 3 years which give new hope to the utility of this pathway in the treatment of hypertension. BI 689648 is a new ASI with a 150-fold selectivity for CYP11B2 which was developed in cyno monkeys, shown to have good oral bioavailability, but has not yet been studied in humans [47]. LY3045697 is another selective CYP11B2 ASI which was studied in a small phase I trial of 51 human subjects and has good safety, tolerability, and pharmacological endpoints, but has not yet been studied for hemodynamic outcomes [48••]. RO6836191 is the most recent ASI developed and studied in a phase I trial with a similar favorable pharmacological profile, but currently has no scheduled phase II trial [49•].

Finerenone

The two main adverse reactions to spironolactone are hyperkalemia and anti-androgenic side effects. Finerenone, formerly BAY 94-8862, was recently developed as an alternative to spironolactone and was designed as a mineralocorticoid antagonist with specificity for cardiac over renal and adrenal receptors [50]. Early trials showed comparable reduced levels of biomarker stress reduction with lower incidence of worsening renal function or hyperkalemia when compared with spironolactone [50]. Finerenone is actively being studied in heart failure, and two recent randomized trials have shown a greater reduction in markers of LV strain when compared with eplerenone with less adverse events, but were not powered to demonstrate a difference in blood pressure as a primary outcome. Both trials however demonstrated a

reduction in blood pressure with increasing doses of finerenone [51•, 52].

Neprilysin Inhibition

Neprilysin, formerly neutral endopeptidase 24.11, is an enzyme important in the degradation of vasoactive peptides such as atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP), and Endothelin [53]. LCZ696 is a combination medication of sacubitril, a neprilysin inhibitor, and valsartan, an angiotensin receptor blocker (ARB). The result is a reduction in vasodilatory peptide degradation with a simultaneous attenuation of vasoconstrictive effectors. The landmark PARADIGM-HF trial published in 2014 showed a significant mortality benefit independent of blood pressure reduction in patients with heart failure and reduced ejection fraction when compared with enalapril [54]. As a result, LCZ696, commercially known as Entresto, is widely known as the newest component of heart failure medication therapy. Prior to PARADIGM-HF though, LCZ696 was studied as an anti-hypertensive, and it is still being evaluated for this in many ongoing trials [55, 56]. Supasyndh et al. recently completed a 52-week follow-up of Asian patients treated with LCZ696 and found a decrease in systolic blood pressure (SBP) of 24.7 mmHg from baseline [57]. Kario et al. studied LCZ696 in a small cohort of patients with severe hypertension and found systolic blood pressure reductions of up to 35 mmHg after 8 weeks of treatment [58]. LCZ696 has been shown to be more effective at systolic blood pressure reduction than comparable doses of either valsartan at 8 weeks (− 5.7 mmHg vs. − 3.4 mmHg, $p < 0.05$) or olmesartan at 52 weeks (− 26.1 mmHg vs. − 20.8 mmHg, $p = 0.028$) [59, 60].

Dopamine-Beta-Hydroxylase Inhibitors

The sympathetic nervous system plays a key role in vasoreactivity, and peripheral adrenergic receptors have long been the target for anti-hypertensive pharmacological therapy with medications such as beta-blockers. Noradrenaline, one of the main vasoactive catecholamines within this system, is generated from the precursor dopamine by dopamine-beta-hydroxylase (DBH). Traditionally, targeting the biosynthesis of noradrenaline and dopamine has been avoided due to the multifaceted role these neurotransmitters play within the central nervous system and the potential for serious adverse events. Recently though, peripherally selective DBH inhibitors have been developed which decrease the peripheral production of noradrenaline without significantly impacting their central counterpart (Fig. 2).

Etamicastat was the first peripherally selective DBH inhibitor developed and has been shown to decrease the noradrenaline to dopamine ratio in the peripheral tissues of rats without crossing the blood brain barrier [61]. It is orally bioavailable and results in a reduction in mean SBP of 37 mmHg after 24 weeks of treatment in spontaneously hypertensive rats [62]. It has been compared with renal denervation in an animal model and results in a more sustained blood reduction after 1 month [63]. Etamicastat has been studied in several phase I trials within the past 5 years with a favorable safety profile and good pharmacodynamics using only once-daily dosing, but has not yet been studied a phase II trial [64••].

Zamicastat, formerly BIA 5-1058, is the newest peripheral selective reversible DBH inhibitor. It also results in a marked reduction in peripheral noradrenaline levels resulting in a dose-dependent reduction in blood pressure with a negligible effect on heart rate. Interestingly, it also results in cholesterol improvement and prolonged survival of spontaneously hypertensive rats [65•]. It is currently being studied in a phase I trial under active recruitment [66].

Direct Renin Inhibitors

Aliskiren is a non-peptide orally bioavailable inhibitor of the enzyme renin and was first commercially approved as an anti-hypertensive medication in 2007. It works by binding to the active site on renin and thereby preventing the conversion of angiotensinogen to angiotensin in the RAAS cascade [67]. There was much initial promise in this medication as a novel target within RAAS system, but subsequent trials such as the ALTITUDE trial and more recently the ATMOSPHERE trial showed increased adverse events such as hyperkalemia and renal injury when used in the setting of ACE inhibitors of ARBs [68, 69]. Two large meta-analyses from 2017 looking at 12,222 and 13,395 patients from 13 and 7 randomized controlled trials respectively found no effect of Aliskiren on all-cause mortality and increased adverse events similar to the ATMOSPHERE trial [70, 71]. The main caveat to all of these trials however is that Aliskiren was studied in combination to standard medical therapy often including ACEi or ARB, not as comparative monotherapy. With this consideration, a recent subgroup analysis from the ATMOSPHERE trial compared Aliskiren monotherapy to ACE inhibitor monotherapy and found a trend towards benefit with Aliskiren without any signal for harm [72].

Sodium Absorption Inhibition

With the recognition of the importance of dietary sodium in the pathogenesis of hypertension, a recently explored novel pathway is the inhibition of dietary sodium absorption. The sodium/hydrogen exchanger 3 (NHE3) is a transporter expressed on the brush border of intestinal epithelial cells and is responsible for the exchange of intracellular hydrogen

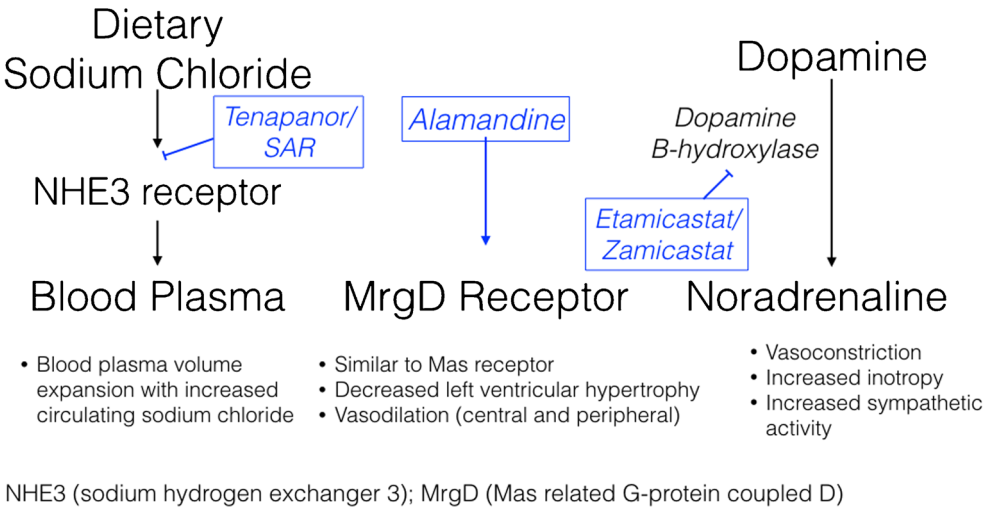

Fig. 2 Emerging treatment pathways in hypertension

for extracellular/intraluminal sodium [73]. Tenapanor is an oral inhibitor of NHE3 with minimal systemic absorption. In preclinical studies of spontaneously hypertensive rats, Tenapanor reduced left ventricular fluid volume, left ventricular hypertrophy, and blood pressure in a dose dependent manner [74]. Tenapanor has been studied in several phase I trials and shows a predictable increase in stool sodium excretion and a decrease in urinary sodium excretion with escalating doses, and no major adverse events [75]. What was also noticed in these phase I trials is that Tenapanour increased stool frequency from one stool daily to two or three stools daily, and softened stool consistency [75]. As a result, it is currently being studied in a phase III trial of constipation predominant irritable bowel syndrome, the results of which were not published as of this writing [76]. Fortunately, other NHE3 inhibitors are still in development with a renewed focus on cardiovascular outcomes, but are still in preclinical stages [77].

Aminopeptidase A Inhibitors

In addition to the peripheral effect on vasculature and renal tissue, vasoactive peptides such as Ang II and their receptors have been localized in the central nervous system (CNS). Angiotensin III (Ang III) is converted from Ang II by the enzyme aminopeptidase A (APA) and plays a prominent role in the central regulation of blood pressure. Intracerebral infusion of Ang III results a sustained blood pressure reduction and a greater response than a comparable infusion of Ang II [78]. Ang II and Ang III both act via the AT1 receptor which is found in the brain, but the affinity of AT1 for Ang III in the CNS is greater than that for Ang II. RB150 is an orally available inhibitor of APA which crosses the blood brain barrier where it is converted to its active compound EC33. When given intravenously to rats, RB150 resulted in decreased Ang II activity and sustained blood pressure reduction over 24 h [79]. RB150 was later found to have good oral bioavailability with a dose-dependent reduction in blood pressure lasting several hours [80]. RB150 was renamed QGC001 and studied in a phase I trial, showing a biological half-life of 3 h, but did not result in blood pressure change in this one dose trial [81••]. QGC001 was studied in a complete phase II trial in 2016 but the results were not published as of this writing [82]. Despite the lack of ongoing human research, RB150 continues to be studied in animal models of hypertension where it shows sustained reduction in blood pressure [83].

Conclusion

Given the many diverse successful medical therapies to treat hypertension, the additional research into new treatment strategies may seem redundant. Yet, despite the multitude of options, there remains a large portion of the population with poorly controlled hypertension. For these reasons, ongoing research into better tolerated and more effective agents is indicated. Pharmacological therapy with drugs such as ACE2 activators, Mas agonists, MrgD agonists, AT2R agonists, aldosterone synthesis inhibitors, neprilysin inhibitors, dopamine-beta-hydroxylase inhibitors, direct renin inhibitors, and aminopeptidase A inhibitors are all potential new strategies to bridge the divide and manage the global burden of hypertension.

Compliance with Ethical Standards

Conflict of Interest The authors declare no conflicts of interest relevant to this manuscript.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- •• Of major importance

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