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REVIEW

New drugs

Therapeutic perspectives in hypertension: novel means for renin–angiotensin–aldosterone system modulation and emerging device-based approaches

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The conventional antihypertensive therapies including renin–angiotensin–aldosterone system antagonists (converting enzyme inhibitors, receptor blockers, renin inhibitors, and mineralocorticoid receptor blockers), diuretics, β-blockers, and calcium channel blockers are variably successful in achieving the challenging target blood pressure values in hypertensive patients. Difficult to treat hypertension is still a commonly observed problem world-wide. A number of drugs are considered to be used as novel therapies for hypertension. Renalase supplementation, vasopeptidase inhibitors, endothelin antagonists, and especially aldosterone antagonists (aldosterone synthase inhibitors and novel selective mineralocorticoid receptor blockers) are considered an option in resistant hypertension. In addition, the aldosterone antagonists as well as (pro)renin receptor blockers or AT_2 receptor agonists might attenuate end-organ damage. This array of medications has now been complemented by a number of new approaches of non-pharmacological strategies including vaccination, genomic interference, controlled breathing, baroreflex activation, and probably most successfully renal denervation techniques. However, the progress on innovative therapies seems to be slow and the problem of resistant hypertension and proper blood pressure control appears to be still persisting. Therefore the regimens of currently available drugs are being fine-tuned, resulting in the establishment of several novel fixed-dose combinations including triple combinations with the aim to facilitate proper blood pressure control. It remains an exciting question which approach will confer the best blood pressure control and risk reduction in this tricky disease.

Keywords Renin–angiotensin–aldosterone system • Endothelin • Controlled breathing • Baroreflex • Renal denervation • Renalase • Fixed combinations

Introduction

Despite the recent and substantial advances in the treatment of hypertension, the majority of patients still remains not optimally controlled; hence, the need for innovative strategies to lower blood pressure (BP). The current BP target values are fairly aggressive, often requiring the addition of a 4th or 5th agent, ultimately taxing the imagination of even the most skilled physician and reducing drug compliance in a large proportion of patients.

Any innovation in antihypertensive therapy is generally judged based on: (i) the capability to improve BP control; (ii) the effectiveness in treatment resistant hypertension; (iii) potential for further (beyond BP control) risk reduction, by impact on the associated functional, metabolic, and structural alterations.[1] While this issue is highly debated, the most part falls on the side of tight BP control rather than a specific treatment.[2] Novel approaches to hypertension treatment include: (i) drug-based strategies targeting traditional (e.g. the renin–angiotensin–aldosterone system, RAAS)

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Table 1 Number of selected compounds in development

Mechanism	Approved	In clinical/late preclinical phase	Note
Angiotensin-converting enzyme inhibitors	0	2	Includes imidapril approved in Japan; and NO-releasing enalapril
AT_1 receptor blockers	3	3	Does not include compounds with dual action
Anti RAAS vaccines	0	2	
AT_2 receptor agonists	0	1	
Vasopeptidase inhibitors	0	4	Including compounds with dual action
Aldosterone antagonists	1	3	
Calcium channel blockers	1	1	
β-Blockers	1	0	Includes nebivolol, NO-releasing blocker
Endothelin antagonists	0	3	Including compounds with dual action
Double combinations	7	5	
Triple combinations	3	0	

Number of compounds approved by FDA since 2000 and identified compounds in clinical/late preclinical phase[1] for 1 February 2011.

or less-well studied (e.g. endothelin or renalase) neurohumoral pathways; (ii) unique approaches involving gene and vaccine therapies; and (iii) device-based therapies (baroreceptor sensitization or renal nerve ablation).[1,3,4] We provide an overview of various therapies in development (*Table 1*) and outline prospects how and which of them might impact clinical care.

The renin–angiotensin–aldosterone system

Physiology of the renin–angiotensin–aldosterone system

The pharmacological RAAS inhibition reduces BP and represents a key part of current approaches to cardiovascular (CV) risk reduction. The classical simplified RAAS image has recently turned to a complex network (*Figure 1*). The cascade starts with the renal release of the renin, which cleaves the liver-produced angiotensinogen to angiotensin I (Ang I).[5] Renin may also bind to its (pro)renin receptor (P)RR,[6] that enhances its cleavage activity and activates its inactive precursor, prorenin. However, binding to (P)RR elicits angiotensin-independent effects, such as activation of promyelocytic zinc finger (PLZF), protein-phosphatidylinositol-3-kinase and eventually mitogen-activated protein kinases (MAPKs) resulting in enhanced proteosynthesis, proliferation, and decreased apoptosis.[7–9]

Angiotensin I (Ang I; Ang 1–10) formed by renin activity is hydrolysed by the circulating and locally expressed angiotensin-converting enzyme (ACE) to the active angiotensin II (Ang II; Ang 1–8). Angiotensin-converting enzyme also inactivates bradykinin with its nitric oxide (NO)- and prostacyclin (PGI_2) stimulating and vasodilative activity.[5] Ang II formation may take place independently of ACE via the enzymatic activity of chymase, carboxypeptidase, cathepsin G, or tonin.[10] In fact, Ang I catabolism is even more complex. Neutral endopeptidase (NEP) can cleave Ang I to Ang 1–7,[11] which may be formed by an ACE homologue, ACE2, via Ang 1–9 or directly from Ang II as well.[12] While Ang (1–7) is degraded by ACE to Ang (1–5), Ang II is degraded to Ang III and IV by aminopeptidase A (AMPA) and M (AMPM), respectively.[13] The different cleavage products then elicit various receptor affinities.

Angiotensin type 1 receptor (AT_1R) mediates most of the Ang II effects, which might be partially opposed by type 2 receptor (AT_2R). Angiotensin III (Ang 2–8) displays affinity to AT_1R and AT_2R as well. AT_2R is also activated by Ang (1–9), while Ang (1–7) stimulates the Mas receptor[14] and possibly the AT_2R.[15] Finally, Ang IV (Ang 3–8) activates the AT_4R or insulin-regulated aminopeptidase.[16]

The AT_1R mediates, among others, vasoconstriction, inflammation, myocardial and vascular hypertrophy, and fibrosis. It is one of the triggers [along with adrenocorticotropic hormone (ACTH), antidiuretic hormone, catecholamines, endothelin, serotonin, or Mg^{2+} and K^+ levels] of aldosterone release, which contributes to Na^+ retention and cardiac, vascular, and glomerular remodelling (*Figure 2A*).[17]

The AT_2R, inhibits MAPKs, activates NO/cGMP and phospholipase A2 pathways, mediating thus anti-proliferation, vasodilation, and anti-inflammation.[18–21] The pharmacological stimulation of AT_2R with the recently discovered non-peptide agonist, compound 21, improved myocardial function in rats with myocardial infarction independently of BP effects[22] but along with anti-inflammatory action and NF-κB inhibition.[23]

Mas may also partially antagonize the AT_1R effects. It promotes Akt phosphorylation,[24] NO release,[25] vasodilation,[14] and anti-inflammation.[26] Mas stimulation with a synthetic peptide induced vasorelaxation, reduced BP in spontaneously hypertensive rats (SHR) and showed antiarrhythmic effects[27] suggesting some therapeutic potential.

Finally, AT_4R stimulation results in proinflammatory effects[13] with possible negative impact.

This complex puzzle of the 'novel RAAS' complicates our understanding of mechanisms participating in the effects of RAAS-interfering drugs, but it offers new and promising drug targets, as well; rendering the RAAS far from being fully exploited.

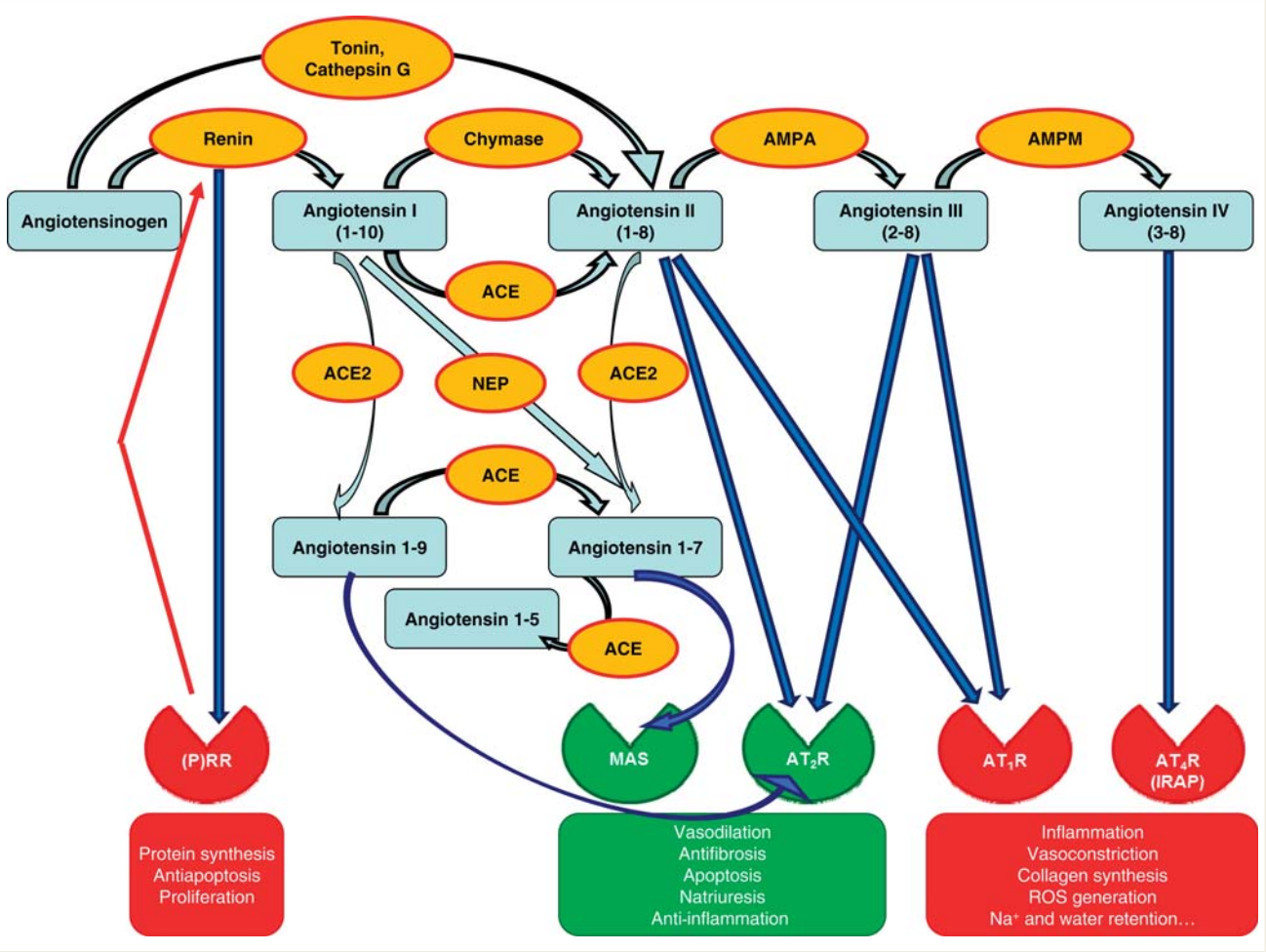

Figure 1 The interplay of recently discovered components of the renin–angiotensin–aldosterone system. The protease renin cleaves angiotensinogen to angiotensin I, which is then hydrolyzed by the circulating and local angiotensin-converting enzyme to the active angiotensin II. Angiotensin II may by alternatively formed by chymase, carboxypeptidase, cathepsin G, or tonin. Angiotensin I might also be directly (by neutral endopeptidase) or indirectly (by angiotensin-converting enzyme and angiotensin-converting enzyme 2 with angiotensin 1–9 as intermmediate product) converted to angiotensin 1–7. Angiotensin 1–7 is degraded by angiotensin-converting enzyme to angiotensin 1–5 while angiotensin II is degraded to angiotensin III and IV by aminopeptidase A and M. Receptors of the renin–angiotensin–aldosterone system include the (pro)renin receptor that enhances the activity of renin, activates prorenin, and elicits angiotensin-independent effects as well. The deleterious effects of renin–angiotensin–aldosterone system activation are ascribed to angiotensin type 1 receptors stimulation by angiotensin II and III. The modestly researched angiotensin type 4 receptor (insulin-regulated aminopeptidase), which is stimulated by angiotensin IV, exerts negative effects too. On the other hand, the stimulation of the angiotensin type 2 receptor, which binds angiotensin II, angiotensin 1–9, and angiotensin III, and Mas receptor, which binds angiotensin 1–7, seem to ellicit beneficial effects. AT_1R, angiotensin type 1 receptor; AT_2R, angiotensin type 2 receptor; AT_4R, angiotensin type 4 receeptor; ACE, angiotensin-converting enzyme; ACE2, angiotensin-converting enzyme 2; AMPA, aminopeptidase A; AMPM, aminopeptidase M; NEP, neutral endopeptidase; IRAP, insulin-regulated aminopeptidase; (P)RR, (pro)renin receptor; ROS, reactive oxygen species.

Current gold standard therapies

Angiotensin-converting enzyme inhibitors and AT_1R blockers are in the centre of the current gold standard for cardioprotective therapies. Their beneficial effects are attributed to inhibition of the undesired AT_1R stimulation and subsequent reduction in vascular tone, BP, aldosterone, vasopressin and catecholamines release, inhibition of inflammation, and attenuation of cell growth. There is a clear evidence for this approach given by clinical trials with ACE-Inhibitors (CAPP[28], STOP-2[29], HOPE[30]) and AT_1R blockers (LIFE[31], VALUE[32]). The later leave the AT_2R unopposed for on-going Ang II stimulation and do not interfere with bradykinin catabolism, which is held responsible for the development of angioedema after ACE inhibition. When telmisartan was compared with ramipril (ONTARGET) it was non-inferior in terms of efficacy and better tolerated (lower incidence of dry cough and angioedema) in high-risk patients.[33] Both ACE-Inhibitors and AT_1R antagonists reduce the onset of new diabetes mellitus[34,35] and some AT_1R blockers, i.e. telmisartan or losartan with its metabolite

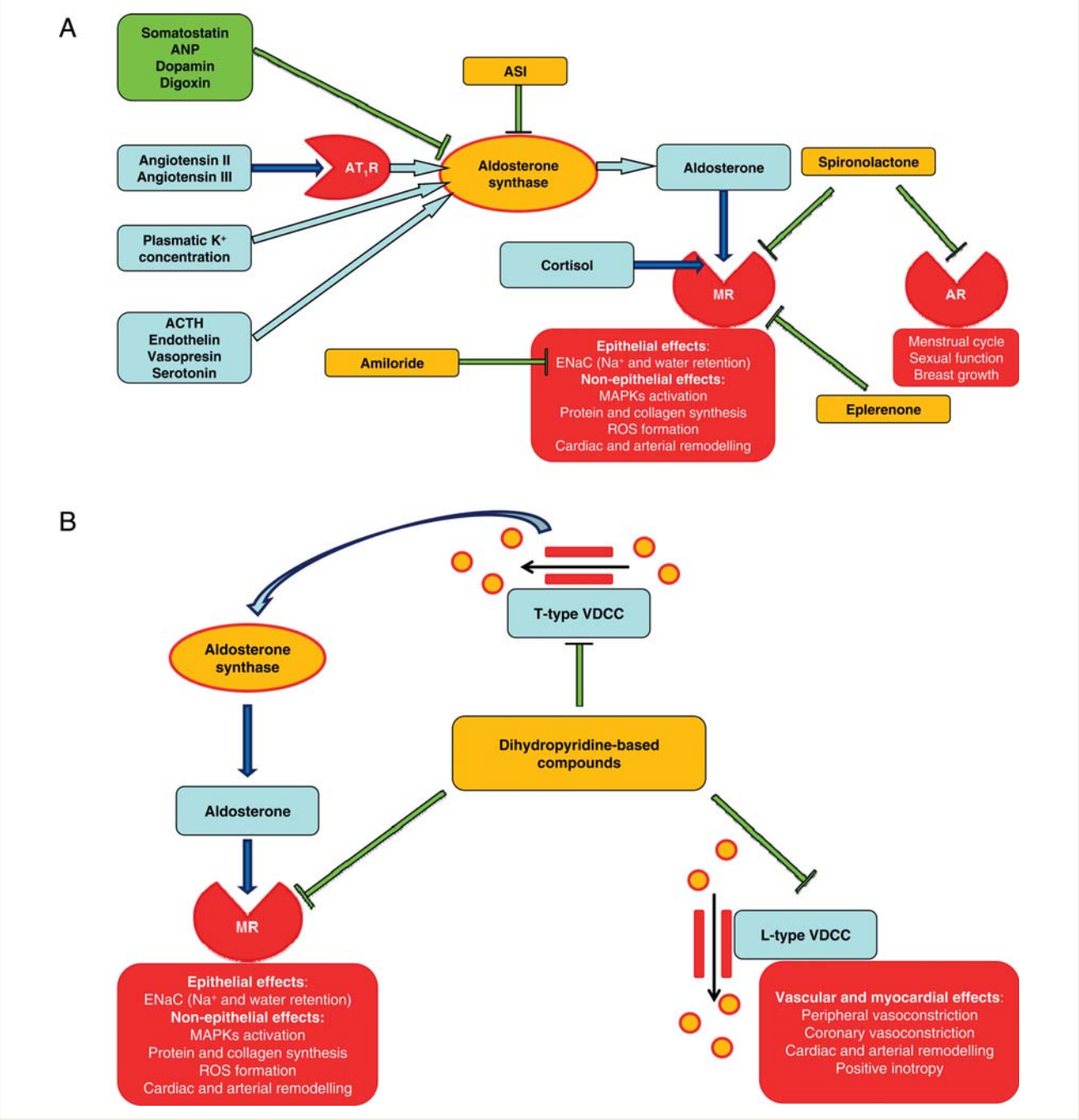

Figure 2 The therapeutic options for aldosterone antagonism. Aldosterone synthase is activated by several factors including angiotensin type 1 receptor stimulation, adrenocorticotropin release and high plasmatic K^+ concentrations. The synthetized aldosterone activates the mineralocorticoid receptor with its epithelial and non-epithelial effects. The epithelial effects include the activation of epithelial Na^+ channel with subsequent Na^+ and water retention; while the non-epithelial effects are participate in tissue remodelling and organ damage. In low aldosterone conditions, the mineralocorticoid receptor might be activated by cortisol as well. The traditional aldosterone antagonist spironolactone antagonises not only the mineralocorticoid receptor receptors but also the androgenic receptors leading to its anti-androgenic side. More recent therapeutic interventions include the inhibition of aldosterone by aldosterone synthase inhibitors; more selective (compared with spironolactone) blockade of mineralocorticoid receptor by eplerenone and finally epithelial Na^+ channel blockade by amiloride. (*A*) Recently several dihydropyridine calcium channel blockers were reported to antagonize the mineralocorticoid receptor and to partially block T-type voltage-dependent calcium channels in addition to the blockade of L-type voltage-dependent calcium channel. Therofore, the dihydropyridine structure might be exploited to design non-steroid compounds with dual aldosterone antagonism $\pm$ L-type voltage-dependent calcium channel blockade (*B*). ACTH, adrenocorticotropic hormone; AR, androgen receptor; ANP, atrial natriuretic peptide; ASI, aldosterone synthase inhibitors; AT1R, angiotensin type 1 receptor; ENaC, epithelial sodium channel; MAPK, mitogen-activated protein kinase; MR, mineralcorticoid receptor; ROS, reactive oxygen species; VDCC, voltage-dependent calcium channel.

EXP 3179, might offer even more metabolic protection as they have peroxisome proliferator-activated receptor-γ activating properties.[36,37]

Further search for a benefit beyond AT_1R antagonism can be expected to lead to devising multifunctional agents that combine AT_1R blocking activity with a NO-releasing moiety, NEP inhibition, or endothelin antagonism.[38]

Renin as a target

Renin, catalysing the rate limiting step in the RAAS cascade, represents a very attractive therapeutic target that was recently exploited by the introduction of the first-in-class selective renin inhibitor, aliskiren. Renin inhibition is indeed associated with the attenuation of Ang I and Ang II levels[39] and BP reduction.[40] Aliskiren reduced BP comparably to β-blockers1,[41] diuretics,[42] ACE–Inhibitors,[43,44] and AT_1R blockers.[40,45] The possible benefit in renin inhibition might reside in the attenuation of plasma renin activity which is increased by ACE inhibition or AT_1R blockade.[46] On the other hand, the high renin levels after aliskiren treatment[47] might escape from renin inhibition and aliskiren may not prevent binding of renin to the (P)RR.[48] A large clinical study programme, named Aspire Higher, is currently underway to determine whether aliskiren treatment ameliorates target-organ damage and positively affects CV morbidity and mortality.

The far from optimal pharmacokinetic properties of aliskiren (2–7% bioavailability)[39] and a ceiling dose of 300 mg daily (due to gastrointestinal irritation) invite novel agents in this class to the pipelines.

Prorenin receptor

The binding of (pro)renin to the (P)RR[6] up regulates the transforming growth factor-β1, plasminogen activator inhibitor-1, fibronectin, and collagen expression,[49] enhances protosynthesis, proliferation, and decreases apoptosis;[7,8] beside the effects on (pro)renin catalytic efficiency itself. Because aliskiren does not inhibit the activation of the (P)RR by (pro)renin[48,50] the specific blockade of (P)RR could not only reduce the enzymatic activity but also prevent some Ang-independent effects of renin. A handling region peptide (HRP) inhibiting the binding of prorenin to (P)RR, completely abolished diabetic nephropathy[51] even in AT_1R knockout mice.[52] It also reduced cardiac fibrosis in stroke-prone SHR[53] and—as observed by an independent group—reduced cardiac hypertrophy and fibrosis in SHR fed high-salt diet.[54] Moreover, the effects on left ventricular hypertrophy in diabetic SHR were additive with the effects of imidapril and seemed to be independent of Ang II levels.[55] However, in rats overexpressing renin and angiotensinogen, the HRP failed to ameliorate target-organ damage in contrast to aliskiren.[56] These partially contradictory data might be explained by different models (the HRP were only effective in low-renin conditions[57,58]) or by degradation/insufficient bioavailability of the decoys. Furthermore, beneficial effects of the HRP *in vivo* were shown in a model of metabolic syndrome[59] as well as regarding diabetic retinopathy.[60,61]

The specificity of HRP binding to the (P)RR was recently shown by label-free interaction analysis.[62] Nevertheless, some authors suggest, that HRP might be in fact a partial agonist on the (P)RR,[63] while others reported that the HRP effects might be (P)RR-independent (HRP did not inhibit renin binding and signalling and it was binding even to cells not expressing the (P)RR *in vitro*).[56]

The development of a non-peptide (P)RR antagonist (i.e. a renin/prorenin receptor blocker, RERB) could shed more light on the role of (P)RR in the development of CV damage and on the potential of its therapeutic inhibition.[9] Finally, RERBs might also exert beneficial effects in cancer considering, e.g. the proproliferative effects of the (P)RR[8] and the seminal observation that this receptor is essential for Wnt signalling.[64]

Vasopeptidase inhibitors

Beside ACE there are other metallopeptidases that convert vasoactive substances, such as ACE2, NEP, or endothelin-converting enzyme (ECE-1). Recent findings indicate a great potential for combined ACE/ECE inhibitors,[65] but most research was devoted to the role of NEP and the therapeutic potential of its inhibition. Neutral endopeptidase substrates belong to vasodilators as well as vasoconstrictors and the effect of NEP inhibition on BP is therefore very modest and variable.[66] On the other hand, the effect of reduced degradation of vasodilative substances after NEP inhibition might prevail in conditions, when the formation or action of the vasoconstrictors is already blocked. In addition, the design of molecules inhibiting both ACE and NEP is very feasible. One of the most studied vasopeptidase inhibitors, omapatrilat, reduced BP in several models of experimental hypertension[67–69] as well as in hypertensive subjects,[70] similarly to sampatrilat.[71] The trials OCTAVE and OVERTURE supported the benefit of ACE/NEP inhibition in hypertension and heart failure, but they reported a higher incidence of angioedema in patients on dual inhibition.[72,73] The most likely explanation is the convergence of both vasopeptidases on bradykinin degradation.[66] Therefore the dual AT_1R/NEP antagonism (angiotensin receptor and neprilysin inhibitors, ARNI) could show a more favourable tolerance profile. Indeed, LCZ696, a first-in-class ARNI, reduced BP additionally to the effect of valsartan, without being associated with occurrence of angioedema in a Phase II study in mild to moderate hypertensive patients.[74] Furthermore, ARNIs cause increased natriuretic peptide concentrations. In primates, natriuretic peptides lead to lipolysis, a fact that might be therapeutically exploited but that also calls for careful characterization of these effects.[75]

Aldosterone receptor antagonists

Spironolactone and eplerenone are mineralocorticoid-receptor blocking agents (MRAs) used for to block the epithelial and non-epithelial actions of aldosterone. These compounds reduce BP,[76–78] diminish urine protein excretion,[79,80] and confer CV gain in heart failure apparently independently of volume alterations.[81–83] The use of MRAs in the treatment of hypertension and, in particular, resistant hypertension has stepped up over the past decade with the growing appreciation for the role of aldosteronism in this disease state.[84,85] In addition, there is an evolving understanding of aldosterone as a downstream effector for some BP-independent Ang II-mediated unfavourable effects.[86]

The BP reduction after spironolactone is conferred similarly in hypertensives with and without primary aldosteronism (though here higher dose is required), independently of ethnicity and urinary aldosterone excretion and it occurs within weeks and

persists indefinitely.[76] Spironolactone might also reduce the apnoea-hypopnea index in patients with resistant hypertension and sleep apnoea.[87] In head-to-head comparison with spironolactone, eplerenone shows comparable BP reduction in the treatment of essential or hyperaldosteronism-associated hypertension.[77,88,89] However, the mg-for-mg BP-lowering effect of eplerenone is lower than that of spironolactone, with 200 mg eplerenone b.i.d. required to achieve BP reduction comparable with 50 mg spironolactone b.i.d. (that produces 1.3–2 times greater reduction than same eplerenone dosage).[77,90]

Spironolactone has gained considerable traction for use in resistant hypertension, but its poor selectivity for mineralocorticoid receptors (MR) often results in progesterone and testosterone-dependent adverse effects, such as loss of libido, menstrual irregularities, painful enlargement of the breasts with nipple tenderness, and gynaecomastia. Eplerenone is much less frequently associated with these adverse conditions and might serve as a substitute for spironolactone in patients with gynaecomastia.[89] However, hyperkalaemia (possibly life threatening) occurs with all MRAs and should always be anticipated.[90]

Recently, some Ca^{2+} channel blockers were reported to antagonize the MR as well.[91] This action, specific to dihydropyridine derivates (e.g. nimodipine), might explain their beneficial effect on cerebral ischaemia and stroke.[91] Molecules with dual action on MR and Ca^{2+} channels might represent a novel and interesting approach to reduce BP and prevent/treat hypertensive end-organ damage. Moreover, they antagonized the MR even in S810L mutant form that is insensitive to spironolactone or eplerenone.[91] This finding highlighted the possibility to develop dihydropyridines with more potent and selective action on the MR. Some such compounds (WO2005097118; DE102005034267, BR-4628) are already in development[91–93] and they might evolve to a putative non-steroid generation of MRAs.

Aldosterone synthase inhibitors

Another approach to antagonise aldosterone is to inhibit its formation and hence prevent the reactive increase in aldosterone levels and their MR-independent effects. Several aldosterone synthase (CYP11B2) inhibitors are being developed.

Fadrozole, an aromatase inhibitor or its dextroenantiomer (FAD286) has been shown to inhibit aldosterone synthase and to reduce mortality, cardiac hypertrophy, albuminuria, cell infiltration, and matrix deposition in the kidney in double transgenic renin rats (dTGR), yet without a profound effect on BP.[94] Similarly in Dahl salt-sensitive rats: intracerebroventricularly applied spironolactone fully eliminated the salt-diet-related increase in BP; whereas, FAD286 only prevented 30 mmHg of the 50 mmHg increase.[95] FAD286 and MRAs comparably reduced hypertrophy and interstitial fibrosis of the kidney and heart induced by Ang II and a high-salt intake.[96]

Another agent, LCI699, reduced 24 h-ambulatory systolic BP by −4.1 mmHg after 4 weeks of treatment but it effectively suppressed supine plasma aldosterone concentrations in a trial on 14 patients with primary aldosteronism. Although, plasma cortisol concentrations did not change, the ACTH concentrations were elevated, the plasma cortisol response to an ACTH stimulation was blunted and the plasma potassium concentration was increased.[97]

The clinical goal for the aldosterone-synthase inhibitors is to be as good as MRAs for BP reduction but better tolerated. The available information would suggest that LC1699 is but modestly effective in patients with primary aldosteronism[97] while 1 mg LCI699 was not superior in BP reduction to eplerenone 50 mg in patients with stage 1 and 2 hypertension.[98] Future studies constructing a full dose–response relationship could determine the clinical significance of LCI699 effect on cortisol homeostasis, and categorize any BP-independent organ-specific effects.[99,100] However, the development of LCI699 was stopped in the 2nd quarter of 2010 in favour of seeking more specific inhibitors.

Besides being reported to antagonize the MR,[91] several dihydropyridine Ca^{2+} channel blockers block T-type channel as well, which brings upon the inhibition of aldosterone synthesis *in vitro*.[101–103] However, the specificity and potency for aldosterone synthase blockade *in vivo* is difficult to estimate. Nevertheless, the dihydropiridine structure might be the base for the development of novel molecules that dually block aldosterone synthase and MR for more potent aldosterone antagonism ± they inhibit the L-type Ca^{2+} channel for more pronounced antihypertensive effects (*Figure 2B*).

Endothelin system

From the endothelin (ET-1, ET-2, and ET-3) polypeptide family is ET-1, the most clinically pertinent isoform, which was identified in 1988 as a potent vasoconstrictor. It plays a prominent role in fibrogenesis, inflammation, oxidative stress, atherosclerosis, salt and water homeostasis, and pulmonary artery hypertension as well.[104–106]

Endothelin receptor A (ET_A) and B (ET_B) antagonists have been studied in resistant hypertension with darusentan (ET_A/ET_B antagonist) being the one most extensively evaluated.[107,108] In patients with resistant hypertension, darusentan met the end-points for systolic and diastolic BP in the DAR-311 (DORADO) trial,[107] and it produced a greater reduction in mean 24-h systolic and diastolic BP than either placebo or the central α_2-agonist, guanfacine, in the DAR-312 (DORADO-AC) trial.[108] However, there was an unexplained BP reduction at Week 14 in the placebo arm[108] and the development of darusentan has been put on hold.

Endothelin antagonists have only been approved for use in pulmonary artery hypertension and their future for the treatment of hypertension is not particularly bright. The most pronounced sticking points with endothelin antagonists include prominent side-effect profile (salt and water retention and peripheral oedema),[107–110] high teratogenicity potential (FDA Pregnancy Category X), and propensity to dose-dependent transaminitis.[110] Moreover, the results from trials in heart failure, chronic kidney disease, cerebral vasospasm, and erectile dysfunction were not very encouraging.

The most pertinent questions for the next generation of endothelin-receptor antagonists are: (i) could superiority to ET_A/ET_B antagonists in BP reduction or tolerance be achieved by designing selective ETA antagonists or dual AT_1R/ET_A antagonists ,[e.g. PS433540[111] (Ligand Pharmaceuticals (San Diego, CA, USA))]; (ii) will these molecules have a differing dose range for BP-dependent

and -independent tissue effects; (iii) will, in these compounds, the dose-dependent oedema still limit reaching a truly effective dose; (iv) might these drugs compete with aldosterone antagonists, which are now fast becoming the treatment of choice for resistant hypertension?

Renalase system

Recently, in an extensive search for vasoactive kidney-related proteins, a novel catecholamine peptidase, renalase, was discovered.[112] Its basal plasmatic activity is very low, but it can be increased by catecholamines,[113] which it in turn metabolizes.[112] Kidneys are probably the major source of circulating renalase as in subnephrectomized rats or in patients with end-stage renal failure the renalase production in the heart, muscle, or liver could not compensate the deficit of kidney-produced renalase.[112,113] Renalase down-regulation or knock-out is associated with increased catecholamine levels, BP and higher susceptibility to ischaemic myocardial damage,[114–116] which are prevented by supplementation with recombinant renalase.[116] Because one renalase polymorphism was associated with essential hypertension[117] and increased CV risk in patients with coronary heart disease,[115] certain patients might be identified that could especially benefit from renalase substitution.

Although some concerns due to the metabolization of the renal vasodilator dopamine by renalase[118] were raised, no alterations in renal function were observed in renalase knock-outs supplemented with recombinant enzyme.[116] Regardless of the therapeutic potential and safety of renalase administration, its discovery might have provided a novel important pathophysiological link between the kidney, sympathetic tone, and BP.

Gene-based therapies

The pharmacological approaches, including the investigational ones, represent 'only' a possible treatment option for hypertension. With complete genome sequenced and other advances in genetics and genetic manipulations there is a search for longer-lasting solution for hypertension meaning better patient compliance, 24-h BP control and possible cost reduction. Some data are encouraging. Overexpression of ACE2 and AT_2R delivered in viral vectors reduced cardiac remodelling[119] and potentiated BP control by losartan[120] in rats with chronic Ang II infusion. Adenoviral transfer of endothelial NO-synthase and kallikrein genes improved endothelial dysfunction[121] and cardiac remodelling[122] in SHR. Even more promising results were reported with suppression of vasoconstrictor expression by the use of cDNA antisense. In SHR, virally delivered antisense cDNA against ACE[123] and AT_1R[124] reduced respective gene expression and attenuated BP. The achieved effects were sustained (from 2 weeks up to 9 weeks), but the major concern is the safety and feasibility of using virus-based delivery systems.

On the other hand a delivery of kallikrein gene in pure plasmid cDNA p.o. reduced BP in SHR but only for 3–5 days.[125] The need for repeated delivery would increase the risk of unfavourable immunologic reactions and also compromise the expected long-lasting effect. Alternative delivery systems include the use of antisense oligodeoxynucleotides and small interfering (si)RNA. Oligodeoxynucleotides against AT_1R reduced BP for 18 days in TGRs,[126] and oligodeoxynucleotides against angiotensinogen for 5 days in SHR.[127] Small interfering RNA against the prepro-thyrotropin-releasing hormone in obesity-induced hypertensive rats reduced BP for at least 24 days.[128] Intraventricularly administered oligodeoxynucleotides targeting renin mRNA reduced BP for 2 days in SHR.[129]

Although being exciting, until more safe and reliable methods of nucleic acid transfer are established, gene-based therapies are unlikely to offer substantial advantage over pharmacological therapies and will rather provide a valuable experimental tool.

Vaccine-based strategies

An immunological approach might offer similar advantages to those expected from gene-based strategies. Recently, two antihypertensive vaccines were developed: PMD3117 against Ang I and Cyt006 against Ang II. Despite some excitement the results were rather disappointing. Although Cyt006 reduced BP in SHR,[130] it achieved inferior BP reduction (9/4 mmHg)[131] compared with conventional antihypertensives. In further studies Cyt006 failed to reproduce this BP reduction, despite shorter dosing intervals and higher antibody titres,[132] and PMD3117 did not decrease BP, despite some degree of RAAS blockade.[133] In addition, the proposed vaccination at Week 0, 4, and 12[131] or 0, 2, 4, 6, and 10[132] might not be appealing enough to improve patient compliance. On the other hand, while previous anti-renin vaccinations were associated with severe kidney disease,[134,135] PMD3117 and Cyt006 were well tolerated in Phase I study[130,133] and Cyt006 also blunted early morning surge in BP.[131]

Thus, the vaccination approach seems feasible and might lead to more effective vaccines or their preventive employment against CV diseases.

Novel device-based approaches

Controlled breathing

Yoga, meditation, and music decrease sympathetic nervous system activity, sensitize arterial and cardiopulmonary baroreceptors and in so doing reduce BP lability and elevated resting BP values. Similarly, slow breathing (<10b.p.m.), especially with a component of prolonged exhalation, reduced sympathetic nerve traffic while increasing parasympathetic activity and lowered BP.[136–138]

Slow breathing can be achieved by systems that coach patients to coordinate their breathing with music, which gradually entrains the respiratory rate downward. The systems require two 15-min sessions daily, endeavouring to achieve at least 45 min of slow breathing time per week. A stored record of the session can be used to assess the patients' adherence. While there are no known contraindications and no reported adverse events, this technique requires a fair amount of discipline and some patients may view pill taking for BP control to be less time-consuming. Moreover, poor hearing (frequent in the elderly) complicates use of this device and a persisting BP-lowering effect seems unlikely. Therefore, the device might find its use as an adjunctive

antihypertensive treatment complementing other pharmacological and/or non-pharmacological interventions.[139,140]

All in all, the published information on this device is sparse and the reported studies lack the comparison to techniques such as meditative relaxation to estimate the contribution of a placebo effect to the BP response. The suitable candidates for this therapy might include: (i) the pre-hypertensive or mildly hypertensives, with small BP reductions required; (ii) white coat or labile hypertensives where behavioural feedback may minimize the alerting reaction; (iii) as a last resort in patients with resistant hypertension and/or those with multiple medication sensitivities/intolerances; (iv) in patients who seek a greater degree of empowerment in managing their hypertension.[141] But still, more persuasive evidence is needed before device guided breathing can be more generally recommended for BP reduction.

Renal sympathetic denervation

Renal nerve ablation has been advanced as a means to interrupting the varied mechanistic pathways by which the kidney affects BP.[142,143] Recently, a percutaneous, catheter-based radiofrequency ablation for renal sympathetic denervation has been developed.[4,144]

This procedure has been evaluated in a cohort study of 45-treated patients with treatment resistant hypertension (baseline BP of 177 ± 20/101 ± 15 mmHg). Office BPs after the procedure were reduced by −14/−10, −21/−10, −22/−11, and −27/−17 mm Hg at 1, 3, 6, and 12 months, respectively with few adverse events.[145]

In another trial Symplicity-2, the safety and effectiveness of catheter-based renal denervation for reduction of BP was assessed in 106 patients with resistant hypertension (baseline BP of 178/96 mm). Office-based BP measurements in the renal denervation group fell by 32 ± 23/12 ± 11 mmHg, whereas they did not differ from baseline in the control group; again with no serious procedure-related or device-related complications in this study.[146]

This procedure hold considerable promise for the patients with resistant hypertension but the specific baseline predictors of success and head-to-head comparisons with other drugs, such as aldosterone antagonists, are yet to be determined.[147]

Baroreceptor activation

The concept of treating hypertension by prolonged electrical activation of the carotid baroreflex has existed since the mid-1960s when clinical studies were initiated in patients with severe hypertension refractory to medication.[148–150] Recently, the development of the three-component Rheos® Hypertension System has resurrected this approach.[151–154]

In the Rheos® DEBuT-HT trial on 45 patients, 72% of 18 patients (baseline BP of 193 ± 36/111 ± 20 mmHg and heart rate of 74 ± 13 b.p.m.) treated for 58 ± 6 months achieved at least a 30-mmHg drop in systolic BP at 4 years (−53 ± 9 mmHg) and the average number of antihypertensive medications used fell from 5.0 to 3.4.[155,156]

Currently, the most rigorous study on the Rheos® device is underway.[157] The Rheos® Pivotal Trial (NCT00442286) is an FDA-approved randomized, double-blind, parallel design phase III trial with 267 enrolled patients who meet the systolic criteria for stage 2 drug-resistant hypertension in up to 50 sites in the USA and Europe.[157] Its current goal is to demonstrate the device's efficacy (i.e. BP reduction >10 mmHg 6 months and 1 year after activation) and acute and long-term safety during implantation and activation periods.[157] Preliminary subgroup results at 6 months post-implant show a 33.7/15.3 mmHg reduction in systolic/diastolic BP compared with pre-implant BP values ($P < 0.001$).[158]

Design optimization will likely be needed to make the device a more market-ready treatment option and will involve surgical technique refinement, improvements in equipment and, in particular, extending battery longevity, and/or developing a unilaterally implantable device.

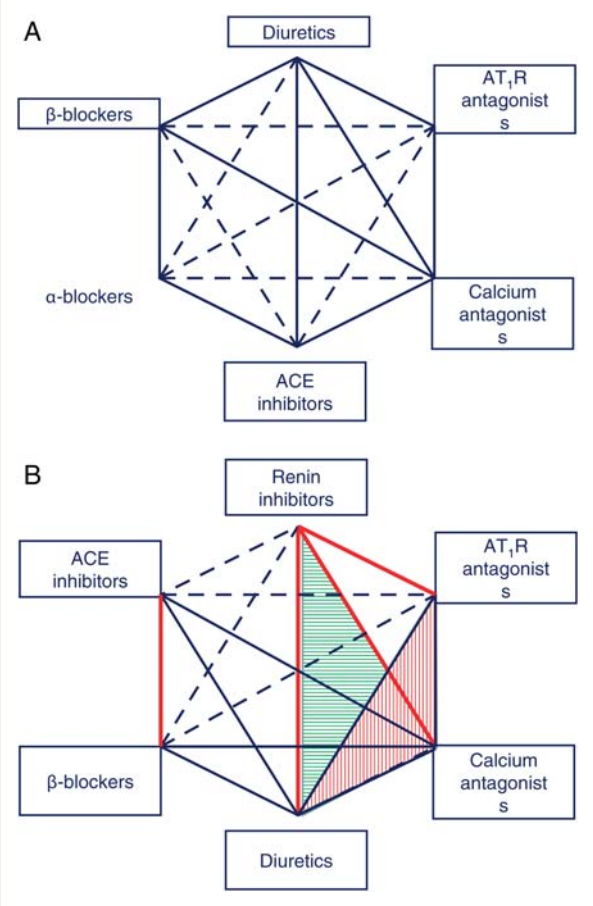

Figure 3 Recent evolution of dual and triple combinations. Schematic representation demonstrating the most rational (thick lines) combinations of classes of antihypertensive agents according to 2003 guidelines for the management of arterial hypertension.[165] (*A*) Adaptation of the upper scheme including direct renin inhibitors (and omitting α-blockers) demonstrating dual (red lines) and triple (patterned triangles) combinations recently approved (since 2003) or in advanced (phase II–III) development in addition to the previously established combinations (blue thick lines). ARBs, angiotensin II type 1 receptor blockers; ACE, angiotensin-converting enzyme. In all recent combinations calcium blockers are represented by amplodipine and diuretics by hydrochlorothiazide. Angiotensin-converting enzyme-inhibitors + β-blockers stand for the combination of lisinopril + carvedilol, which is a combined β/α_1-blocker (*B*).

Fixed-dose combinations

Triple therapies

A considerable legacy, dating to the 1950s, exists for fixed-dose combination therapies. The rationale to this approach has remained constant since that time: combinations reduce BP because each drug blocks different effector pathways or the second drug checks counter-regulatory system activity triggered by the other.[159] In fact most of the hypertensive patients require at least two drugs to achieve the target BP values,[160] as recommended for mild-severe hypertension (≥grade 2) by the current guidelines.[161] The addition of the diuretic hydrochlorothiazide to AT_1R antagonists can markedly enhanced BP reduction[162] and the combination of AT_1R antagonist with Ca^{2+} channel blocker amlodipine was more effective compared with either drug alone.[163] In addition to superior BP control, the addition of AT_1R antagonist might reduce the risk of peripheral oedema caused by amlodipine therapy[163] or hypokalaemia evoked by diuretic administration.[164] Since 2000, 10 new fixed-dose combinations were approved including AT_1R antagonist (or ACE-Inhibitor or renin inhibitor) + hydrochlorothiazide (and/or amlodipine); AT_1R antagonist + renin inhibitor; ACE-Inhibitor + β-blocker; and amlodipine + statin[1,165] and their efficacy and safety has been established. However, the two-drug fixed-dose combination era is now rapidly morphing to three drug combinations. The investigational triple therapies are composed of a RAAS inhibitor, amlodipine, and hydrochlorothiazide.[1,166,167] In hypertensive patients with a mean sitting diastolic BP of >100 mmHg such triple-therapy (valsartan + amlodipine + hydrochlorothiazide) lowered BP by 40/25 mmHg which was significantly more compared with the any two-drug combination (*Figure 3*).[166,168]

Although, unsurprisingly, the triple combinations provided more profound BP reduction and higher BP control rate without compromising the tolerability or safety,[169] the question remains whether combination therapy should be administered in fixed-dose combinations or not. The advantages of single pill regimens are (i) more simple administration, (ii) more rapid achievement of BP goal than by gradual titration; (iii) existing simple and rapid full dose up-titration schemes; (iv) better patient adherence to therapy; (v) potential for fewer non-responders to a three-drug choice. On the other hand, their disadvantages include (i) higher risk of dose-independent adverse reactions, (ii) loss of dose flexibility, with possibly inappropriate dosing,[160,168] and (iii) the inability to introduce a chronotherapeutic approach.[170] Hence, individually tailored therapy is traded for reduced costs and simplification.

More studies on novel combinations including aliskiren as RAAS inhibitor or chlorthalidone as diuretic are on the way and the recommendations on triple therapy should become more specific. After more evidence is provided, patients that will mostly benefit from single-pill regimens can be identified, while in others the therapy may still be individually adjusted.

Conclusions

Difficult to treat hypertension is a commonly observed problem globally. Available, conventional therapies have been the mainstay of therapy for hypertension but still have been variably successful in bringing BP to goal. A number of other drug classes have been used as complementary therapies for BP reduction including central α_2-receptor agonists, peripheral α_1-receptor antagonists, and direct vasodilators. This array of medications has now been complemented by a number of new approaches of a medication, immunologic, and device nature. Many of them are being tested and the basis for their use refined. In addition, therapeutic regimens are being fine-tuned and several novel fixed-dose combinations were recently established. However, therapies such as aldosterone synthase inhibition, endothelin receptor antagonism, and gene and vaccine based-strategies have evolved more slowly than expected and point to the difficulty in bringing a new therapy for hypertension to market.

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