Chapter 5
Novel Molecules

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Abbreviations

C21	Compound 21
cGMP	Cyclic guanosine 3′,5′-monophosphate
COX	Cyclooxygenase
CYP	Cytochrome P-450
ET-1	Endothelin 1
ET-2	Endothelin 2
ET-3	Endothelin 3
ETA	Endothelin receptor type A
ETB	Endothelin receptor type B
ETEs	Epoxyeicosatrienoic acids
ETRA	Endothelin receptor antagonist
FDA	Food and Drug Administration
HETEs	Hydroxyeicosatetraenoic acids
KO	Knockout
LOX	Lipoxygenase
LTs	Leucotrienes
LXs	Lipoxins
MR	Mineralocorticoid receptors
NEP	Neutral endopeptidase
NO	Nitric oxide
sEH	Soluble epoxide hydrolase
sGC	Soluble guanylyl cyclase

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Table 5.1 Novel antihypertensive treatments

Blood pressure mechanism	Antihypertensive agent
Sympathetic system	Human recombinant renalase
Renin–angiotensin–aldosterone system	Renin inhibitors
	Anti-angiotensin vaccine
	Angiotensin II type 2 receptor agonist
	Aldosterone synthase inhibitor
Natriuretic peptide system	Vasopeptidase inhibitors
Other hormones and autacoids	Stimulators and activators of soluble guanylate cyclase
	Soluble epoxide hydrolase inhibitors
	Endothelin antagonists

Novel Drugs for Hypertension

Effective drugs for hypertension treatment have been available for many years and interventions at several levels in the complex mechanisms regulating arterial blood pressure (BP) have been successful with an acceptable adverse event profile. Target values of BP are difficult to achieve and many patients remain uncontrolled [1] and at high risk of end-organ damage. In the chronic kidney disease (CKD) population, this is especially true and remarkable because it is well known that BP reduction not only will reduce cardiovascular risk but also will improve proteinuria, delaying progression to end-stage renal disease. Newer treatments and novel approaches are constantly under investigation with the intention of enhancing BP control and reducing cardiovascular and renal risk. These novel drugs are being considered as monotherapy or combinations to standard treatment. Here, we will outline selected drugs classified by the BP regulation system they interfere (Table 5.1).

Sympathetic System

Renalase

Renalase is a flavin adenine dinucleotide-dependent amino oxidase secreted almost entirely by the kidney. It metabolizes circulating catecholamines [2], and epinephrine is the principal substrate. The hypotensive effect of the protein has been proved in vitro and in vivo [3]. The inactive enzyme appears to circulate in blood and can be activated by circulating catecholamines or increased BP. Renalase knockout (KO) mice display elevated plasma and urinary catecholamines levels, hypertension, tachycardia, ventricular hypertrophy and inadequate cardiac and renal ischemia tolerance [4]. Animal models have shown that renalase levels increase significantly after renal denervation and this higher plasma level may mediate in part the procedure's BP lowering effect [5]. Recombinant human renalase

(hRenalase1) administered subcutaneously had a systolic and diastolic hypotensive effect, and attenuated hypertension-related cardiac damage in 5/6 nephrectomized rat [6, 7]. Administration of hRenalase1 in KO animals also improved ischemic and toxic renal injury [2]. These findings suggest that renalase represents a novel option for hypertension treatment, but human studies are needed.

Renin–Angiotensin–Aldosterone System

Renin Inhibitors

Aliskiren is the first oral direct renin inhibitor available that has been commercialized in the past years. It is an effective antihypertensive drug with an adverse effect profile similar to angiotensin receptor blockers (ARBs). Since effective drug therapy with angiotensin converting enzyme inhibitors and ARBs is standard of care in many hypertensive and cardiovascular diseases, aliskiren was evaluated as add on therapy.

In the ALTITUDE trial, aliskiren and losartan were tested against losartan alone in diabetic type 2 patients with cardiovascular and renal risk. The trial found no benefit and more hiperkalemic and hypotensive events in the aliskiren group. This chapter concluded that the addition of aliskiren to standard therapy with renin–angiotensin system blockade in type 2 diabetes patients who are at high risk for cardiovascular and renal events is not supported by these data and may even be harmful. Since then, the Food and Drug Administration (FDA) has issued a warning that aliskiren should not be used in this clinical situation.

Many physicians use this drug in resistant hypertensive patients.

Anti-angiotensin Vaccines

Renin–angiotensin system vaccines have been investigated in the past and are still under development. Renin was the first target but the product was associated with autoimmune kidney disease development. An anti-angiotensin I vaccine effectively reduced BP in animal models, but failed to prove efficacy in clinical trials. Anti-angiotensin II and anti-ATR1 vaccines are a matter of interest and current studies. Cyt-006-AngQb reduced BP in animal models and hypertensive patients [8]. Ang II-KLH-immunized mice decreased BP values and cardiac hypertrophy [9]. Anti-ATR 1 ATRQβ-001 reduced BP in Ang II-induced hypertensive mice and spontaneously hypertensive rats without evidence of immune-mediated organ damage [10]. Vaccines seem to be a feasible line of treatment for hypertension with longer dosing intervals than traditional therapies, although more clinical trials are needed and safety profile must be verified.

Angiotensin II Type 2 Receptor Agonist

In humans, angiotensin II has two G protein-coupled receptors: type 1 (AT 1R) and type 2 (AT 2R). Through AT 1R, angiotensin II mediates vasoconstriction, tubular Na reabsorption, modulation of glomerular filtration rate, aldosterone release, collagen synthesis and pro-fibrotic and inflammatory effects [1]. AT 2R mediates opposite actions that lead to vasodilation, anti-proliferation and anti-inflammation via the nitric oxide (NO)/cyclic guanosine 3′,5′-monophosphate (cGMP) pathway, and also phosphatase and phospholipase A2 activation [11]. In pathological states, the expression of AT2R is upregulated in certain tissues, especially during tissular hipoxia [12]. Therefore, pharmacological stimulation of AT2R is an encouraging option for hypertension treatment. Compound 21 (C21) is the first selective non-peptide AT 2R agonist. Animal studies have not shown BP reduction, however, it did reduce arterial stiffness, media collagen deposition, oxidative stress, fibrotic processes, hypertrophic effects on the heart and renal cortex inflammatory cell infiltration [13]. In addition, C21 produced vasodilation, and natriuretic effects, improving renal function [14]. When combined with low-dose ARB, C21 enhanced the antihypertensive effect of the former [13], while this did not occur with higher ARB doses. C21 did not show significant BP reduction as monotherapy but its potential multiple beneficial effects may promote new strategies and combinations in hypertension treatment [11].

Aldosterone Synthase Inhibitors

Aldosterone mediates its effects via mineralocorticoid receptors (MR), but also in an MR-independent fashion. Therefore, in order to act on both mechanisms, aldosterone synthase inhibition has emerged as a new therapeutic target. Early in the 1990s, the nonsteroidal aromatase inhibitor fadrozole showed the potential to induce aldosterone secretion impairment without affecting the glucocorticoid response [15]. Fadrozole's enantiomer FAD286A in animal models decreased plasma and urine aldosterone concentrations, preventing cardiac hypertrophy and fibrosis, albuminuria, renal failure and death [16]. Based on FAD286A, the first orally active aldosterone synthase inhibitor was synthesized, LCI699. In a phase II study, LCI699 was compared with eplerenone and placebo for 8 weeks in subjects with stage 1–2 essential hypertension [17]. Primary end point was reduction in diastolic BP, which was significantly lower, compared with placebo, for LCI699 1 mg once daily and eplerenone 50 mg twice daily in similar magnitude. All doses of LCI699 decreased clinic systolic BP and 24-h ambulatory BP significantly. Patients did not develop signs of hypocortisolism although ≈20% of subjects had suppression of adrenocorticotropic hormone (ACTH)-induced cortisol release. Not serious, hyperkalemia or renal function impairment was reported in LCI699 or eplerenone groups [17]. LCI699 was tested in primary aldosteronism in a single-centre, single-blind, placebo-controlled, sequential, force-titration study [18]. A reduction in plasma

and urinary aldosterone concentration was observed as correction of hypokalemia within the first week of treatment, accompanied by limited effects on BP and sodium-positive balance [18]. Despite clinical benefits on BP control, reduction of circulating aldosterone, enhance sodium excretion, glucocorticoid axis inhibition will limit LCI699 use [19]. More selective compounds could provide advantages; however, complete blockage of aldosterone synthesis could entail potential serious adverse consequences [19].

Natriuretic Peptide System

Vasopeptidase Inhibitors

Vasopeptidase inhibitors are soon to be an upcoming approach to hypertension treatment. Neutral endopeptidase (NEP) catalyzes both vasoconstrictor and vasodilator products. The beneficial effect of NEP inhibition is mediated by increased natriuretic peptide concentration [20], but inhibition of this enzyme alone did not improve clinically relevant outcomes [21]. However, benefits of NEP blockage may become evident when vasoconstrictors such as angiotensin II are reduced by concomitant use of angiotensin-converting enzyme (ACE) inhibitors or ARBs [21, 22]. The dual ACE/NEP inhibition has been associated with increased risk of angioedema [23]. LCZ696 is a combination of an angiotensin II receptor blocker (valsartan) and a neprilysin inhibitor (AHU377). Patients treated with LCZ696 had significant dose-dependent reductions in BP compared with valsartan and AHU377 monotherapy. LCZ696 improved pulse pressure and was safe and well tolerated [21].

Hormones and Autacoids

Stimulators and Activators of Soluble Guanylate Cyclase

NO-induced vasorelaxation is mediated by activation of soluble guanylyl cyclase (sGC) that increases cGMP formation and ultimately a decrease in intracellular calcium and vasodilation. In conditions associated with incremented oxidative stress, NO generation, diminished biological availability can lead to NO donor tolerance with prolonged use [24]. Two classes of compounds that activate sGC by NO-independent pathways are under investigation: sGC stimulators and sGC activators. The sGC stimulator BAY 63-2561 (Riociguat) was tested in a population with mild to moderate pulmonary hypertension and improved pulmonary hemodynamics to a greater extent than inhaled NO. Riociguat significantly reduced systolic BP and systemic vascular resistance [25]. Activators of sGC can increase sGC enzyme activity even when it is oxidized and less responsive to NO [24]. BAY 58-2667 (Cinaciguat)

has been administered to patients with acute decompensated heart failure and proved to lower right atrial pressure, pulmonary and systemic vascular resistance reducing preload and afterload [26].

Both sGC stimulators and sGC activators may represent therapeutic options for pulmonary hypertension, states of chronic endothelial dysfunction such as hypertension and atherosclerosis and in patients with acute heart failure [24].

Soluble Epoxide Hydrolase Inhibitors

Arachidonic acid is metabolized by three principal enzymatic pathways: cyclooxygenase (COX), lipoxygenase (LOX) and cytochrome P-450 (CYP) (Fig. 5.1). Prostaglandins are produced by COX; hydroxyeicosatetraenoic acids (HETEs), lipoxins and leucotrienes by LOX; HETEs are also generated by CYP hydroxylase and epoxyeicosatrienoic acids (ETEs) are originated from CYP epoxygenase [26]. ETEs mediate vasodilation in many vascular beds including coronary, cerebral, kidney, intestine and skeletal muscle by activating large-conductance calcium-activated potassium channels in vascular smooth muscle cells [26]. They also have anti-inflammatory, anti-aggregation and angiogenic properties.

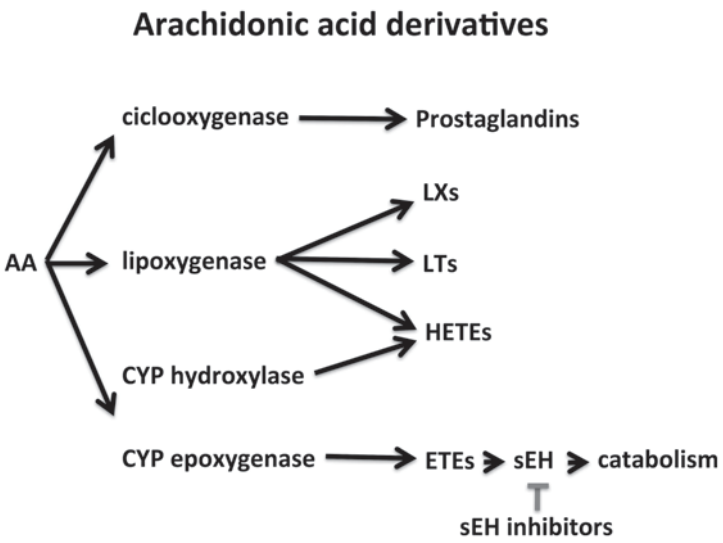

Fig. 5.1 Arachidonic acid derivatives and new potential antihypertensive mechanisms. On the *bottom*, soluble epoxide hydroxylase inhibitors reduce epoxyeicosatrienoic acids degradation and enhance vasodilation in different vascular beds. *AA* arachidonic acid, *COX* cyclooxygenase, *LOX* lipoxygenase, *CYP* cytochrome P-450, *HETEs* hydroxyeicosatetraenoic acids, *LXs* lipoxins, *LTs* leucotrienes, *ETEs* epoxyeicosatrienoic acids

Soluble epoxide hydrolase (sEH) is responsible for ETE catabolism. Inhibition of ETE catabolism increases ETEs levels and enhances their beneficial effects. sEH inhibitors include ureas and amides, among others [27].

In hypertensive animal models, sEH inhibition results in BP reduction, mainly in angiotensin hypertensive mechanisms. Renal vascular and glomerular injury, renal macrophage infiltration and collagen deposition, cerebral ischemia, cardiac hypertrophy, vascular remodelling and atherosclerosis were reduced consistently in these studies [26, 27]. Renal protection seems to be both dependent and independent of the antihypertensive mechanism [28].

In human studies, sEH inhibitor AR9281 did not decrease BP in patients with mild to moderate hypertension [27], but clinical indications of sEH inhibitors may include hypertension-related end-organ damage prevention, metabolic disease treatment, chronic inflammatory therapy and vascular remodelling prevention. Tumour proliferation due to angiogenic properties, pulmonary vasculature vasoconstriction and blood clotting alterations may be unwanted considerable adverse effects [28].

Endothelin Antagonists

Endothelin is a product of endothelial cells with vasoconstrictor effects. Three isoforms are recognized in humans: endothelin 1 (ET-1), endothelin 2 (ET-2) and endothelin 3 (ET-3), but ET-1 is of major interest in the hypertension field. ET-1 secretion is stimulated by angiotensin II and many other agonists and factors including hypoxia [29] and mediates vasoconstriction, inflammation and vascular remodelling. ET-1 has two receptors: type A (ETA) which is prevalent in vascular smooth muscle cells and type B (ETB) mostly in endothelial cells. Darusentan, an endothelin receptor antagonist (ETRA), is approved for pulmonary hypertension treatment [30]. This drug has been utilized to treat resistant hypertension patients in DORADO [31] and DORADO-AC [32] clinical trials. Although BP reductions were achieved darusentan, BP reduction was also observed in the placebo arm in DORADO-AC patients. Sitaxsentan, an ETA antagonist, reduced BP and proteinuria in CKD but glomerular filtration rate diminished by 9 ml/min after 6 weeks of treatment [33]. ETRA's main adverse events include fluid retention and peripheral oedema.

Summary

The next decade or two are filled with exciting therapeutic promises that hopefully will be fulfilled. As we advance knowledge in genetics and pathophysiology of hypertension, novel insights and molecules will be tested in the quest of lowering BP and protecting vital organs. In this diverse array of mechanisms that can influence BP, several appear to be essential and drugs blocking or inhibiting them will be pivotal in the near future.

Stimulators and activators of soluble guanylate cyclase and aldosterone synthase inhibitors have the best potential in the hypertension field. Renin inhibitors, vasopeptidase inhibitors and endothelin antagonists will need newer compounds that surpass and improve results obtained by the original drugs.

References

1. Paulis L, Unger T. Novel therapeutic targets for hypertension. Nat Rev Cardiol. 2010; 7(8):431–41.
2. Xu J, Wang P, Velazquez H, Yao X, Li Y, Wu Y, et al. Renalase is a novel, soluble monoamine oxidase that regulates cardiac function and blood pressure. J Clin Ivest. 2005;115:1275–80.
3. Desir GV, Tang L, Wang P, Li G, Sampaio Maia B, Quelhas-Santos J, et al. Renalase lowers ambulatory blood pressure by metabolizing circulating catecholamines. J Am Heart Assoc. 2012;1:e002634.
4. Wu Y, Xu J, Velazquez H, Wang P, Li G, Liu D, Sampaio-Maia B, Quelhas-Santos J, et al. Renalase deficiency aggravates ischemic myocardial damage. Kidney Int. 2011;79(8):853–60.
5. Jiang W, Guo Y, Tan L, Tang X, Yang Q, Yang K. Impact of renal denervation on renalase expression in adult rats with spontaneous hypertension. Exp Ther Med. 2012;4(3):493–6.
6. Baraka A, El Ghotny S. Cardioprotective effect of renalase in 5/6 nephrectomized rats. J Cardiovasc Pharmacol Ther. 2012;17(4):412–6.
7. Desir GV, Wang L, Peixoto AJ. Human renalase: a review of its biology, function, and implications for hypertension. J Am Soc Hypertens. 2012;6(6):417–26.
8. Tissot AC, Maurer P, Nussberger J, Sabat R, Pfister T, Ignatenko S, et al. Effect of immunisation against angiotensin II with CYT006-AngQb on ambulatory blood pressure: a double-blind, randomised, placebo-controlled phase IIa study. Lancet. 2008;371:821–7.
9. Nakagami F, Koriyama H, Nakagami H, Osako MK, Shimamura M, Kyutoku M, et al. Decrease in blood pressure and regression of cardiovascular complications by angiotensin II vaccine in mice. PLoS ONE. 2013;8(3):e60493.
10. Chen X, Qiu Z, Yang S, Ding D, Chen F, Zhou Y, et al. Effectiveness and safety of a therapeutic vaccine against angiotensin II receptor yype 1 in hypertensive animals. Hypertension. 2013;61:408–16.
11. Foulquier S, Steckelingd UM, Unger T. Impact of the AT2 receptor agonist C21 on blood pressure and beyond. Curr Hypertens Rep. 2012;14:403–9.
12. Steckelings UM, Kaschina E, Unger T. The AT2 receptor-a matter of love and hate. Peptides. 2005;26:1401–9.
13. Rehman A, Leibowitz A, Yamamoto N, Rautureau Y, Paradise P, Schiffrin EL. Angiotensin type 2 receptor agonist compound 21 reduces vascular injury and myocardial fibrosis in stroke-prone spontaneously hypertensive rats. Hypertension. 2012;59:291–9.
14. Hilliard LM, Jones ES, Steckelings UM, Unger T, Widdop RE, Denton KM. Sex-specific influence of angiotensin type 2 receptor stimulation on renal function: a novel therapeutic target for hypertension. Hypertension. 2012;59:409–14.
15. Trunet PF, Mueller P, Girard F, Aupetit B, Bhatnagar AS, Zognbi F, et al. Effects of fadrozole hydrochloride on aldosterone secretion in healthy male subjects. J Clin Endocrinol Metab. 1992;74:571–6.
16. Fiebeler A, Nussberger J, Shagdarsuren E, Rong S, Hilfenhaus G, Al-Saadi N, et al. Aldosterone synthase inhibitor ameliorates angiotensin II-induced organ damage. Circulation. 2005;111:3087–94.
17. Calhoun DA, White WB, Krum H, Guo W, Bermann G, Trapani A, et al. Effects of a novel aldosterone synthase inhibitor for treatment of primary hypertension: results of a randomised, double-blind, placebo- and active-controlled phase 2 trial. Circulation. 2011;124:1945–55.

18. Amar L, Azizi M, Menard J, Peyrard S, Watson C, Plouin PF. Aldosterone synthase inhibition with LCI699: a proof-of-concept study in patients with primary aldosteronism. Hypertension. 2010;56:831–8.
19. Azizi M, Amar L, Menard J. Aldosterone synthase inhibitions in humans. Nephrol Dial Transplant. 2013;28:36–43.
20. Campbell JC. Vasopeptidase inhibition: a double-edged sword? Hypertension. 2003;41:383–9.
21. Ruilope LM, Dukat A, Bohm M, Lacourciere Y, Gong J, Lefkowitz MP. Blood-pressure reduction with LCZ696, a novel dual-acting inhibitor of the angiotensin II receptor and neprilysin: a randomised, double-blind, placebo-controlled, active comparator study. Lancet. 2010;375:1255–66.
22. Unger T, Paulis L, Sica DA. Therapeutic perspectives in hypertension: novel means for renin-angiotensin-aldosterone system modulation and emerging device-based approaches. Eur Heart J. 2011;32: 2739–47.
23. Kostis JB, Packer M, Black HR, Schmieder R, Henry D, Levy E. Omapatrilat and enalapril in patients with hypertension: the omapatrilat cardiovascular treatment vs. enalapril (OCTAVE) trial. Am J Hypertens. 2004;17:103–111.
24. Nossaman B, Pankey E, Kadowitz P. Stimulators and activators of soluble guanylate cyclase: review and potential therapeutic indications. Crit Care Res Pract. 2012;2012:290805.
25. Grimminger F, Weimann G, Frey R, Voswinckel R, Thamm M, Bölkow D, et al. First acute haemodynamic study of soluble guanylate cyclase stimulator riociguat in pulmonary hypertension. Eur Respir J. 2009;33(4):785–92.
26. Imig JD. Epoxides and soluble epoxi hydrolase in cardiovascular physiology. Physiol Rev. 2011;92:101–30.
27. Shen HC, Hammock BD. Discovery of inhibitors of soluble epoxi hydrolase: a target with multiple potential therapeutic indications. J Med Chem. 2012;55(5):1789–808.
28. Imig JD, Hammock BD. Soluble epoxi hydrolase as a therapeutic target for cardiovascular diseases. Nat Rev Drug Discov. 2009;8(10):794–805.
29. Rautureau Y, Schiffrin EL. Endothelin in hypertension: an update. Curr Opin Nephrol Hypertens. 2012;21(2):128–36.
30. Barton M, Yanagisawa M. Endothelin: 20 years from discovery to therapy. Can J Physiol Pharmacol. 2008;86(8):485–98.
31. Weber MA, Black H, Bakris G, Krum H, Linas S, Weiss R, et al. A selective endothelin-receptor antagonist to reduce blood pressure in patients with treatment-resistant hypertension: a randomised, double-blind, placebo-controlled trial. Lancet. 2009;374:1423–31.
32. Bakris GL, Lindholm LH, Black H, Krum H, Linas S, Linseman JV, et al. Divergent results using clinic and ambulatory blood pressures: report of a darusentan-resistant hypertension trial. Hypertension. 2010;56:824–30.
33. Dhaun N, MacIntyre IM, Kerr D, Melville V, Johnston NR, Haughie S, et al. Selective endothelin-a receptor antagonism reduces proteinuria, blood pressure, and arterial stiffness in chronic proteinuric kidney disease. Hypertension. 2011;57:772–9.