The latest development of antihypertensive medication

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Abstract. Hypertension is the most common risk factor for cardiovascular disease, stroke, renal failure, and death. Recent drug monitoring studies found non-adherence to BP lowering therapy in 25% to 65% of patients with apparent treatment-resistant hypertension (TRH). This review focuses on the latest development of antihypertensive medication, such as vasopeptidase inhibitors, aldosterone synthase inhibitors, Soluble Epoxide Hydrolase Inhibitors, agonists of natriuretic peptide receptor, Vasoactive Intestinal Peptide Receptor Agonist, a novel mineralocorticoid receptor antagonist, inhibitors of aminopeptidase A, dopamine β-hydroxylase inhibitor, intestinal Na+/H+ exchanger 3 inhibitor and other agents.

1. Introduction

Hypertension is a problem health in the world that can cause damage to the kidney, heart, and brain, cause 7.5 million deaths. It accounts for 57 million of disability-adjusted life years. Around 25% of adults in the United States of America had hypertension in 2011-2012. Prevalence between male and female is similar but the prevalence increases with age.[1-4] In this review, we will discuss the latest development of antihypertensive medication.

2. New Drug Classes

2.1. Anti-Aldosterone

The principal effector of aldosterone action is the mineralocorticoid receptor (MRs), it could stimulate expression of Na channels, increases Na and H2O reabsorption, K loss, that cause volume expanded form of hypertension. Activation of MRs in extra-adrenal tissues can promote hypertension and CVD by upregulating NADPH oxidase and increasing production of reactive oxygen species (ROS), that reduces the bioavailability of nitric oxide, lead to endothelial dysfunction and vascular disease. Anti-Aldosterone Agents will inhibit this pathway as antihypertensive hypertension strategy.[5,6]

2.2. Mineralocorticoid Receptor Antagonists(MRAs)

Due to lack of selectivity for the MR, the use of Spironolactone has been limited. Spironolactone has significant progestogenic and antiandrogenic activity, that have adverse effects. Eplerenone, more selective MRAs, is less potent and, that reduce the efficacy and need twice daily dosing.[7,8]

Finerenone, a nonsteroidal MRA is more selective than spironolactone, and has a greater affinity than eplerenone, and does not have an effect on L-type Calcium channel.[9]

2.3. Aldosterone Synthase Inhibitors(ASIs)

The first orally active aldosterone synthase inhibitor to be developed for human use, LCI699 has a similar structure with FAD286, the dextroenantiomer of the nonsteroidal aromatase inhibitor fadrozole. It decreases plasma and urine aldosterone concentrations, increases plasma renin activity, and prevents target organ damage in animal models of hypertension and HF dose-dependently.[10,11]

2.4. Activators of the Angiotensin-Converting Enzyme2/ Angiotensin(1–7)/ MAS Receptor Axis

The carboxypeptidase ACE2 converts the decapeptide angiotensin I (Ang I) to the Ang(1–9) nonapeptide and the octapeptideAng II to the Ang(1–7) heptapeptide. Amplification of ACE2/Ang(1–7)/Mas signaling opposes the effects of the classical RAS and lowers BP and prevents or reverses related target organ damage.

Novel approaches to RAS inhibition, are being evaluated in trials. Activation of the more recently described counter regulatory RAS pathway decreases blood pressure (BP) and target organ damage, and drugs that activate this pathway include ACE2 activators, Ang (1–7) analogs, AT2 receptor agonists, peptide and nonpeptide activators of the Mas receptor, and alamandine complexed with cyclodextrin.[12,13]

2.5. Aminopeptidase Inhibitors

Aminopeptidase A(APA) and aminopeptidase N, are involved in brain Ang II and III metabolism ,and have similar affinities for Ang II receptors and both peptides stimulate pressor responses by activating sympathetic nervous system activity, inhibiting the baroreflex at the level of the nucleus tractus solitarius and increasing release of arginine vasopressin into the circulation. Studies using selective APA (EC33) and aminopeptidase N (PC18) inhibitors have demonstrated that brain Ang III (not Ang II, as in the periphery) have a role in BP control, make APA a potential hypertension therapeutic target.[14,15]

2.6. Angiotensin Receptor–Neprilysin Inhibitors

The first-in-class angiotensin receptor–neprilysin inhibitor LCZ696 is a novel single molecule composed of the neprilysin inhibitor prodrug AHU377 (sacubitril) and the ARB valsartan in a 1:1 ratio.[16]

2.7. Natriuretic Peptide Receptor Agonists (NPR-A)

NPR-A inhibit degradation of endogenous natriuretic peptides for the treatment of HF and refractory or resistant hypertension. The NPR-A PL-3994 is a synthetic molecule that contains an amino acid mimetic and has reduced affinity for the natriuretic peptide clearance receptor (NPR-C), increased resistance to neprilysin, has prolonged half-life after subcutaneous administration. A phase I trial of a single subcutaneous dose of PL-3994 showed increased natriuresis and diuresis, elevation in plasma cyclic guanosine monophosphate levels, and reduction in systemic BP compared with placebo. A phase II trial in volunteers with hypertension that had ≥1 antihypertensive drugs showed a reduction in systemic BP. PL-3994 act synergistically with ACE inhibitors.[17,18]

2.8. Vasopeptidase Inhibitors

The zinc metalloprotease neprilysin degrades the natriuretic peptides atrial natriuretic peptide (ANP), BNP, and urodilatin. Neprilysin inhibition increased the levels of circulating natriuretic peptide, that promoted natriuresis, vasodilation, RAAS inhibition, reduced sympathetic drive, and antiproliferative and antihypertrophic effects on the heart and vasculature.[19,20]

2.9. Soluble Epoxide Hydrolase Inhibitors (s-EH)

Soluble epoxide hydrolase (s-EH) catalyzes the conversion of multiple lipid epoxides to the corresponding dihydroxy lipids. Substrates of s-EH include members of the arachidonic acid family, and the effects of s-EH inhibitors have been attributed to increased epoxyeicosatrienoic acid levels. Inhibitors of s-EH can cause lower BP, prevent and reverse pressure overload-induced cardiac hypertrophy, attenuate ischemic and ischemia-reperfusion injury of the brain and heart, prevent atherosclerosis and aneurysm formation, and attenuate insulin resistance in animal models.[21,22]

2.10. Vasoactive Intestinal Peptide (VIP) Receptor Agonist

VIP is a neuropeptide with vasodilator and positive inotropic/chronotropic effect. It is mediated by the G-protein-coupled receptors VPAC1 and VPAC 2. Deficiency in VIP and alterations in properties of VPAC1 and 2 were described in various forms of the cardiopulmonary disease, and VIP is a therapeutic target for hypertension. Vasomera is a stable form of VIP, selective for VPAC2. It has been developed by fusing an analog of VIP with the elastin-like polypeptide.[23,24]

2.11. Intestinal Na^+/H^+ Exchanger 3 Inhibitor

Electroneutral Na^+/H^+exchangers, such as NHE2, NHE3, and NHE8, transport sodium from the intestinal lumen into enterocytes. NHE3 (SLC9A3) is inhibited selectively by tenapanor, which does not cross the intestinal barrier. Tenapanor decreases urinary sodium excretion and increases stool sodium in humans. A study in rat showed that Tenapanor reversed extracellular volume expansion, lowers BP, and reduces albuminuria and cardiac and renal injury.[25,26]

2.12. Dopamine β-hydroxylase Inhibitor

Dopamine β-hydroxylase (DβH), is the enzyme that catalyzes the dopamine hydroxylation to form noradrenaline. It becomes a therapeutic target for hypertension and cardiovascular disorders with sympathetic activation. Inhibition of DβH have a gradual sympathetic slowdown and increases dopamine availability, thus causing renal vasodilation, natriuresis, and dieresis.[27,28]

3. Anti-hypertension in liver disease

The prevalence of essential hypertension in with cirrhosis patients was around 15 %.[29,30] Arterial hypertension is not frequently found in liver disease [31], but alcoholic liver disease (ALD) patients often have high blood pressure and need antihypertensive treatment.[31,32]

The plasma concentrations of antihypertensive drugs metabolized in the liver may increase in patients with advanced liver cirrhosis, therefore the reduction of the dose and prolongation of administration intervals is necessary at initial use. Drug-induced Liver disease agent such as labetalol and methyldopa must not be given in liver dysfunction.[33]

Ehnert et al found that antihypertensives may both positively and negatively influence chronic liver disease progression. They investigated amlodipine, captopril, furosemide, metoprolol, propranolol, and spironolactone on alcohol-induced damage to human hepatocytes (hHeps). They found that antihypertensives could influence the progression of liver fibrosis by modulating HO-1 activity in liver cells. The effect of amlodipine and propranolol was only observed at high concentrations close to the LC50. Meanwhile, captopril, metoprolol, or spironolactone, at low concentrations already have protecting effect. Furosemide-induced profibrogenic TGF-β1 signaling, that facilitated liver fibrosis in vivo.[32] Therefore, the choice of antihypertensive used is important in patients with ALD as they could both promote or reduce liver fibrosis, which needs further investigation.

4. Conclusion

There were several studies of antihypertensive medication that have a specific target therapy for the development of new drugs. Further studies are needed for the use in clinical practice.

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