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Novel therapeutic strategies in the management of arterial hypertension

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ABSTRACT

Essential hypertension is a disease with a major impact on health worldwide, thus control of blood pressure seems to be a key component of cardiovascular disease prevention. Despite considerable advances in the treatment of hypertension, effective management remains poor and new strategies to control high blood pressure and cardiovascular risk reduction are required. These seem to be divided into two major categories: those seeking to advance blood pressure-lowering efficacy of already existing agents, and others related to novel approaches, both pharmacological and non-pharmacological. Moreover, numerous clinical trials have evaluated the use of nutritional supplements in the prevention of cardiovascular diseases and in achievement of optimal blood pressure control. Additionally, the advent of interventional techniques, such as carotid baroreceptor stimulation and renal ablation of sympathetic nerve activity, seems to be proved effective in cases where medical management and lifestyle modifications are insufficient. Genetic technology, which has advanced tremendously over the past few years, could assist novel treatment options in hypertensive patients, such as RNA interference targeting hypertension-related genes. However, continued efforts must progress in these areas and the effects of therapeutic strategies in hypertensive patients need to be further explored in larger trials over a longer period of time.

Contents

1. Introduction

Essential hypertension is an important public health challenge because of its high prevalence, which is estimated to rise to 29%, by the year 2025 (Androulakis et al., 2009; Vedanthan & Fuster, 2009). Current anti-hypertensive treatment, or other agents, such as tetrahydrobiopterin, seems to exert additive cardiovascular benefits, due to their anti-inflammatory and antioxidant properties (Navalkar

Abbreviations: ACE, angiotensin converting enzyme; Ang, Angiotensin; ARBs, angiotensin receptor blockers; AT2R, angiotensin T2 receptor; BH4, Tetrahydrobiopterin; BP, blood pressure; ED, endothelial dysfunction; eNOS, endothelial nitric-oxide synthase; PDE5Is, phosphodiesterase-5 inhibitors; RAS, renin–angiotensin system; SHR, spontaneously hypertensive rats; SPAK, Ste20-related proline alanine-rich kinase; WNK, with-no-K(Lys).

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et al., 2001; Channon, 2004; Milionis et al., 2006; Marchesi et al., 2008). Furthermore, novel targets for antihypertensive therapy are also likely to be related with renin–angiotensin system (RAS), such as the stimulation of angiotensin II type 2 receptors and antiangiotensin vaccination (Paulis & Unger, 2010).

Populations of both resistant and difficult-to-treat hypertension have emerged due to cases where polypharmacy strategies fail to regulate blood pressure (BP). Apart from that, chronic use of particular agents has been associated with severe side-effects (Stas et al., 2006). Consequently, novel approaches based on interventional techniques have been developed, such as carotid baroreceptor stimulation and renal ablation of sympathetic nerve activity which may offer a more attractive risk/benefit relationship in the treatment of hypertension (Krum et al., 2011). Ultimately, given the tremendous advances in technology a number of tools are now available for the investigators to examine gene-function relationships which may eventually lead to targeted prevention and treatment strategies.

The present review will provide an overview of advances regarding the treatment of hypertension, giving a particular emphasis on the efficacy of current and novel pharmacological approaches, as well as surgical intervention techniques. Recent discoveries and approaches will also be discussed, including the RNA interference and a new signaling cascade which hopefully will provide novel druggable targets.

2. Pharmacological agents targeting the renin–angiotensin system (RAS)

2.1. Classic anti-hypertensive agents

The renin–angiotensin–aldosterone system plays a major role in BP regulation. However, it comprises multiple actions beyond vasoconstriction and fluid regulation, such as inflammation and stimulation of cell growth, thus its pharmacological inhibition remains the current 'gold standard' therapy in the management of hypertension and in reducing the risk of cardiovascular events.

According to clinical and experimental data, current anti-hypertensive agents (Table 1), such as angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), beta-blockers and calcium antagonists seem to exert additive anti-inflammatory effects in hypertensive patients (Savoia & Schiffrin, 2006). Notably, vascular inflammation could be a potential therapeutic target, given data suggesting that hypertension-associated chronic inflammation may be linked to increased cardiovascular risk. Moreover, given the potential reciprocal relationship between endothelial dysfunction and hypertension, specific agents which improve vascular function, could be proved useful in the management of arterial hypertension (Tousoulis et al., 2010).

Significant data suggest that ACE inhibitors and ARBs potentially decrease the risk of cardiovascular disease given their ability to prevent or reverse endothelial dysfunction, atherosclerosis and vascular inflammation (Böhm, 2007; Tousoulis et al., 2008; Stefanadi et al., 2010). Specifically, treatment with ramipril reversed impaired endothelial function and decreased the expression of proinflammatory cytokines and adhesion molecules, even in the absence of arterial hypertension (Brili et al., 2008). Also, in a double-blind randomized trial perindopril normalized the hemodynamic responses to L-arginine, ameliorating endothelial function of hypertensive patients (Giugliano et al., 1998). RAS blockade with ACE inhibitors and ARBs further decrease microalbuminuria, and thus, improve renal prognosis. Given the central role of angiotensin II in endothelial dysfunction, RAS blockade provides a rational explanation for the effect on endothelial dysfunction and microalbuminuria (Ruilope et al., 2007). Moreover, according to a recent prospective study, renal vascular resistance, renal plasma flow, and renal endothelial function (indicated by basal nitric oxide activity) improved during treatment with telmisartan or ramipril (Ritt et al., 2009). Telmisartan potentially is accompanied by cardioprotective properties, such as reduction of arterial stiffness, vascular distensibility and endothelial dysfunction in hypertension (Grassi et al., 2008). Moreover, there is evidence suggesting that valsartan reserved endothelial dysfunction through both NO-dependent and independent pathways (Tzemos et al., 2009).

On the other hand, calcium antagonists also seem to possess interesting properties with regards to the management of arterial hypertension. Specifically, nifedipine in a randomized, double-blind trial which enrolled 264 patients with mild-to-moderate hypertension, tended to reduce inter-cellular adhesion molecule-1 and E-selectin and von Willebrand factor levels (Rosei et al., 2005). Notably, clevidipine a late-generation dihydropyridine calcium channel antagonist is approved for the reduction of blood pressure when oral therapy is not feasible or desirable (Deeks et al., 2009). Moreover, data indicate that in terms of controlling acutely elevated BP, clevidipine is more effective than sodium nitroprusside or nitroglycerin in the perioperative setting, and has similar efficacy to that of nicardipine in the postoperative setting. In seven Phase III trials, clevidipine was effective in controlling BP in the settings of perioperative cardiac surgery and severe hypertension and demonstrated a tolerability profile similar to that of placebo, regarding adverse events (Nguyen et al., 2010).

2.2. Angiotensin T2 receptor agonists

Undoubtedly, advances have been made regarding the approval for clinical use of numerous ACE inhibitors and angiotensin II type 1 blockers. In fact, the most recently recognized agents of these categories

Table 1
Novel pharmacological agents targeting the renin–angiotensin system.

Agent	Category	Action	Properties
Azilsartan	ARB with PPAR-γ activity	Blocks the action of angiotensin II and stimulates the peroxisome proliferator-activated receptor γ	↓BP
Imidapril	ACE inhibitor	Inhibit angiotensin-converting enzyme important to the formation of angiotensin II	↓BP
Clevidipine	Ca channel blocker	Dihydropyridine L-type calcium channel blocker selectively relaxing smooth muscle cells that line small arteries	Effective in controlling BP in perioperative cardiac surgery and severe hypertension
Compound 21	AT2 receptor agonist	Non-peptide, selective AT2 receptor agonist	↓BP, improves post-MI systolic and diastolic function
CYT006	Vaccination	Virus-like particles covalently coupled to angiotensin II	↓BP, no serious adverse events
PMD3117	Vaccination	12-amino-acid analogue of Ang I	Controversial regarding lowering BP ability
NCX899	NO donor	NO-releasing derivative of enalapril	Effective in preventing cardiovascular changes induced by acute NOS inhibition
Naproxcinod	NO donor	COX-inhibiting nitric oxide donators	↓BP, eliminates constricting effects of COX inhibition in the vasculature
BH4	Tetrahydrobiopterin	Required cofactor for the NOS enzymes	↓BP, vascular inflammation, oxidative stress

BP: blood pressure; ARB: angiotensin receptor blocker; PPAR-γ: peroxisome proliferator-activated receptor γ; MI: myocardial infarction; AT2: Angiotensin II type 2; NO: nitric oxide; ACE: angiotensin converting enzyme; COX: cyclo-oxygenase; PPAR-γ: Peroxisome proliferator-activated receptor gamma; AT: angiotensin.