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New Generation Calcium Channel Blockers in Hypertensive Treatment

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Abstract

During a couple of decades, a number of antihypertensive drugs have been developed, and the choice of hypertension treatment has been expanded. Among antihypertensive drugs, calcium channel blockers, which inhibit L-type voltage-gated calcium channels, are potent vasodilators, and have been used as a first- or second-line drug. Dihydropyridine-class calcium channel blockers are categorized into three generations according to the length of activity, and long-acting calcium channel blockers cause less activation of sympathetic nervous system, and are reported to offer beneficial action compared with short-action agents. Furthermore, novel types of calcium channel blockers have been developed that possess the blocking action on other calcium channel subtypes (T- and N-type), and exert agent-specific action apart from their class effects, such as the effects on heart rate and renin/aldosterone release. These additional benefits conferred by T/N-type calcium channel blockade are anticipated to provide organ protective actions in the treatment of hypertension, in addition to the blood pressure-lowering effect of L-type calcium channel blockade. In conclusion, novel calcium channel blockers with sustained activity and T/N-type calcium channel blocking action could provide more beneficial effects than classical blockers, and may expand the clinical utility of these agents.

Keywords

N-type calcium channels; T-type calcium channels; tachycardia; heart failure; renal protection

INTRODUCTION

Hypertension is one of the most important risk factors for cardiovascular diseases, including cerebral infarction, ischemic heart diseases and heart failure. Indeed, a 5–6 mmHg decrement in diastolic blood pressure is demonstrated to reduce the risk of stroke and coronary heart disease [1,2]. Several classes of antihypertensive agents have been in clinical use, including diuretics, α-blockers, β-blockers, angiotensin converting enzyme (ACE) inhibitors, angiotensin II type 1 receptor blockers (ARB), and organic calcium channel blockers (CCBs). Among them, CCBs exert potent antihypertensive action and are widely used as a first line antihypertensive drug with few contraindication [3–7]. Traditionally, CCBs exert dilator action on vascular smooth muscle cells by inhibiting calcium entry through L-type calcium channels. Recently, novel types of CCBs have been developed that express unique characteristics. Thus, certain CCBs manifest blocking activity on N- (cilnidipine) and/or T- (mibefradil and

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efonidipine) type calcium channels as well as L-type channels, and it is surmised that these properties produce additional benefits associated with reductions in cardiovascular events and renal injury. For example, the blockade of N-type or T-type calcium channels in cardiac pacemaker cells may suppress heart rates, which could therefore reduce cardiac events and improve survival [8,9]. Although this premise appears intriguing, it remains to be established whether these subclasses of calcium channels contribute to the development of cardiovascular events in a clinical setting.

As there are many interesting review articles of calcium antagonists [10], we attempt to characterize the action of various CCBs based on the target channel subclasses, especially on T-type and N-type channels in this review. Furthermore, the roles of these properties in the development of organ injury, including heart and kidney, are also assessed.

1. CLASSIFICATION OF CALCIUM CHANNELS AND CCBS

The voltage-gated calcium channel consists of 4 subunits, α1, α2-δ, β and γ. An α1 subunit is the dominant component of the calcium channels and constitutes pore structure for ion conduction. Ten different α1 subunits have been reported and each of them has specific distribution and ion conductance of its channels (Table 1). These distinct subunits characterize the channel properties of L-, N-, T-, P-, Q- and R-type calcium channels [11,12]. Of these channels, L-type calcium channels are the main targets of the CCB. Either α_{1S} ($Ca_v1.1$), α_{1C} ($Ca_v1.2$), α_{1D} ($Ca_v1.3$) or α_{1F} ($Ca_v1.4$) subunit is a component of L-type calcium channels. The α_1 subunits of T-type channels include α_{1G} ($Ca_v3.1$), α_{1H} ($Ca_v3.2$) and α_{1I} ($Ca_v3.3$). The α_{1I} distributes in the brain, and α_{1G} in the brain, sinoatrial node, atrioventricular node, Purkinje fiber and along the nerve. The α_{1H} subunits prevail in sinoatrial node, atrioventricular node, Purkinje fiber, brain, kidney and liver. The subunits of P/Q, N and R-type channels are α_{1A} ($Ca_v2.1$), α_{1B} ($Ca_v2.2$), and α_{1E} ($Ca_v2.3$), and these channels are distributed in the brain, neuron, and pituitary gland [13].

Based on the chemical structure, CCBs are categorized into 3 subgroups; benzothiazepines (e.g., diltiazem and clenazem), phenylalkylamines (e.g., verapamil and gallopamil) and dihydropyridines (e.g., nifedipine, nicardipine, felodipine, amlodipine, aranidipine, azelnidipine, cilnidipine, efonidipine, manidipine and nilvadipine). The differences in chemical structures would provide heterogeneity in the action of these agents. All CCBs block the calcium influx by binding to the α1 subunit [14], and inhibit cell excitability. Benzothiazepines [15] and dihydropyridines binds to the specific amino acid residue of the α1 subunit exposed to the cell surface. In contrast, phenylalkylamines bind to the specific region of the α1 subunit located at the inner surface of the cell membrane [16,17]. Benzothiazepines and phenylalkylamines have negative inotropic or chronotropic effect, whereas dihydropyridines do not show negative chronotropic effect because of its reflex tachycardia due to peripheral vasodilation.

Although the CCB inhibits calcium currents through L-type calcium channels, some CCBs possess the ability to block other calcium channels. Mibefradil is a well-known T-type calcium channel blocker, and has a similar structure with phenylalkylamines, but possesses weak L-type calcium channel blocking activity [18]. Efonidipine is developed as a long acting dihydropyridine-class CCB, and found to possess both L-type and T-type calcium channel blocking action [19]. Recently, some of dihydropyridines, including benidipine [20], nilvadipine [21], and aranidipine [22] are also reported to possess T-type calcium channel blocking activity. Cilnidipine is a recently developed CCB, and possesses both L- and N-type calcium channel blocking activity [23]. Since N-type calcium is distributed along the nerve and in the brain, cilnidipine is anticipated to exert specific action on nerve activity, such as inhibition of the sympathetic nervous system. In this regard, recent studies have demonstrated that amlodipine possesses N-type calcium channel blocking action [24].

Based on the difference in the formula and the length of their action, dihydropyridine-class CCBs are clinically classified to 1st, 2nd, and 3rd generations [25]. The first generation drugs are the original formula of nifedipine, nicardipine, verapamil, and diltiazem. Second generation drugs have better pharmacokinetic profile that encompasses longer action than 1st generation drugs and enhanced vascular selectivity. They are subdivided to 2 groups; slow release formula (e.g., nifedipine SR (slow release), felodipine ER (extended release) and diltiazem SR) and newer chemical structures (e.g., benidipine, manidipine, nilvadipine and nitrendipine). The third generation drugs have defined as long acting drugs, and two distinct types of CCBs belong to this generation; one is characterized by a sustained blood concentration with a long half-life. Amlodipine is in the ionized state at a physiological pH and combines slowly with the receptor and binds firmly to various tissue compartments [26]. The other category is characterized by lipophilic and highly histotropic properties,(e.g., lercanidipine and lacidipine) which subsequently provides long-acting pharmacokinetics of this agent [26,27]. Azelnidipine is also lipophilic [28,29] and has the high affinity to vascular tissue [30], and these properties have yielded long activity. In general, longer acting and lipophilic CCBs tend to have slow onsets.

2. CCBS AND THE HEART

Framingham study reported that heart rate is one of the most important factors for the mortality of cardiovascular disease. CASTEL study also reported that heart rate is the strong predictor of the cardiovascular death in men [31]. It was conventionally believed that CCBs were not an appropriate treatment for heart diseases because they elicit the reflex tachycardia associated with excessive decrease in blood pressure, activation of sympathetic nervous system and renin-angiotensin system, cardiac overload and labile hypertension [32–35]. Actually, several lines of clinical studies have reported unfavorable effects of CCBs in the treatment of heart diseases. Boden *et al*. [36] reported that nifedipine increased the heart rate and the incidence of angina pectoris, when compared with β-blockers or nitrate. In The MDPIT Trial Research Group, diltiazem exerted no overall effect on mortality and incidence of reinfarction of the postinfarction patients [37]. Elkayam *et al*. reported that the deterioration of heart failure was higher in the nifedipine-treated group than that of the isosorbide dinitrate-treated group [38]. Furberg *et al*. [39] analyzed 16 randomized trials using nifedipine and reported that the mortality was increased in a dose-dependent manner in these trials. Most of these problems are associated with the use of short acting dihydropyridines and the subsequent occurrence of reflex tachycardia and rapid blood pressure decrease. To counter this confounding issue, novel types of CCBs have been developed.

The first category of the drugs is the CCB with sustained action to avoid reflex tachycardia, and amlodipine, lercanidipine and azelnidipine are included in this class. Controversy attends the impact of CCBs on heart failure. Although lowering blood pressure improves or prevents the development of heart failure, some CCBs are known to deteriorate cardiac function in patients with heart failure. Several lines of clinical trials also have witnessed that newly-developed CCBs prevent the cardiovascular/cerebrovascular events [40–43]. For example, amlodipine is demonstrated to exert salutary action in several clinical trials. In PRAISE study [44], amlodipine improved the morbidity and mortality in the patients with non-ischemic cardiomyopathy, but not the ones with ischemic heart diseases. In PREVENT study, amlodipine retarded the progress of coronary atherosclerosis, and it did not increase the incidence of cardiovascular events [45]. The VALUE study has demonstrated that there is no difference in the incidence of heart failure or stroke between amlodipine- and valsartan-treated patients, and the incidence of myocardial infarction is rather lower in amlodipine-treated group [40]. Amlodipine is also demonstrated to reduce cardiovascular events compared with enalapril and placebo did in the CAMELOT study [46]. Amlodipine is reported to improve the cardiac function in ischemia-reperfusion injury [47] and does not increase the mortality and morbidity

of heart failure patients [41,44]. Recently, ASCOT-BPLA study reported that amlodipine-based regimen reduced the incidences of cardiovascular diseases and inhibited the progress of diabetes compared with that of atenolol-based regimen, though combination of perindopril with amlodipine and that of bendroflumethiazide with atenolol could affect on the results [48]. With regard to other recent CCBs, PATE-Hypertension demonstrated that the incidence of cardiovascular events was not different between manidipine-treated group (27.8/1000) and in delapril-treated group (22.5/1000) [43]. Long-term treatment with azelnidipine is demonstrated to decrease heart rate in hypertensive animal model [49] and in a randomized double-blind study of 46 patients with essential hypertension [29]. Arita *et al*. [50] demonstrated that azelnidipine decreased blood pressure both at rest and at exercise without an increase in cardiac output, heart rate or plasma norepinephrine/epinephrine compared to other antihypertensive agents, including metoprolol, doxazosin, trichlormethiazide and nifedipine.

In accordance with these new antagonists, evidence has been accumulated that sustained nifedipine release tablets whereby nifedipine is gradually released in the gastrointestinal tract offer favorable benefit in patients with cardiovascular disease. For example, in the JMIC-B trial, nifedipine-retard has been as effective as ACE inhibitors in preventing the cardiac events and mortality in patients with hypertension and coronary artery disease [51,52]. Furthermore, although in the ACTION trial, addition of nifedipine GITS to the conventional treatment of angina pectoris has no effect on major cardiovascular event-free survival in patients with stable angina pectoris [51,52], nifedipine GITS significantly reduces the incidence of any stroke or transient ischemic attack and the need for coronary angiography by 21% in normotensives and 16% in hypertensives. Thus, different drug absorption systems (nifedipine *vs*. nifedipine-retard/nifedipine-GITS) may influence the vulnerability to cardiovascular events.

The second group is characterized by the possession of the blocking action on multiple calcium channels in addition to L-type calcium channels, into which group cilnidipine and efonidipine are categorized. It is well established that verapamil and diltiazem can be used for rate control, because both agents block calcium-dependent conduction in the AV node and effective for supraventricular tachycardia. In contrast, dihydropyridines have been reported to cause tachycardia since they potentially activate sympathetic nervous system [53].

Furthermore, T-type calcium channels are distributed in pacemaker cells, atrial cells and Purkinje fibers in the heart [54], although L-type calcium channel are mostly found in the myocardium. Under the condition of atrial fibrillation, L-type calcium channels and sodium channels are down-regulated and inactivated [55], whereas calcium influx through T-type calcium channels remains active [56]. This small persistent calcium influx from T-type calcium channels would induce calcium overload and is responsible for the mechanism for continuous atrial fibrillation. Fareh *et al*. [57] reported that mibefradil prevented atrial fibrillation-promoting electrophysiological remodeling by atrial tachycardia in dogs subjected to rapid atrial pacing for 7 days. Masumiya *et al*. [21] reported that efonidipine suppress selectively the later phase of pacemaker depolarization through inhibition of both L- and T-type calcium currents of rabbit sinoatrial node tissue and decreased the heart rate. Indeed, efonidipine has potent negative chronotropic but weak inotropic activity [58]. Ohashi *et al.* [59] have recently demonstrated that efonidipine exerts a more sustained action to prevent atrial electrical remodeling compared with verapamil in dogs underwent rapid atrial pacing. Since atrial fibrillation downregulates L-type calcium channels but maintains T-type calcium channel activity, it is expected that calcium influx is refractory to L-type calcium channel blockade, but more susceptible to T-type channel blockade.

In the clinical studies, several chronotropic and inotropic effects have been reported. Harada *et al*. [9] demonstrated that administration of efonidipine decreased heart rate, reduced

sympathetic nervous activity and enhanced parasympathetic nerve activity in patients with a high heart rate. Using a more T-type-selective calcium channel blocker, mibefradil, Lee *et al*. [60] reported an improvement in treadmill exercise parameters, compared with diltiazem CD in patients with chronic stable angina in the PRIDE trial. Pellizzer *et al*. [61] demonstrated that mibefradil increased parasympathetic nervous system activity, although no differences existed between effect of L- and T-type CCB on sympathetic nervous system activity and baroreflex sensitivity.

It has recently been reported that the increased current of T-type calcium channels is responsible for the progression of heart failure in the myocardium of rat ventricle [62]. Generally, α_{1H} (an α1 subunit of T-type calcium channels) is highly expressed in the embryonal myocardium, and is decreased with the growth of the animal [63]. In contrast, α_{1G} (an α1 subunit of T-type calcium channels) is rarely expressed in the embryonal myocardium. In the myocardium of the UM-X7.1 cardiomyopathic hamster, the expression of α_{1G} subunits is increased, compared with that of the control hamster, and a T-type calcium channel blocker, mibefradil, retards the progression of heart failure [64]. Izumi *et al*. [65] demonstrated that endothelin1 activation increased the T-type calcium current and the expression of the α_{1G} mRNA level in ventricular myocytes in Dahl salt-sensitive rats with heart failure, and these increases were eliminated by the chronic bosentan treatment. Mibefradil is demonstrated to reduce interstitial and perivascular fibrosis and improve cardiac function in myocardial infarction-induced heart failure in rats [66]. Unfortunately, mibefradil caused fatal arrhythmia in MACH-1 study [67], and this arrhythmia is presumably due to the interaction with other drugs that are also metabolized by the cytochrome P-450 3A4 enzyme. Although this interaction is not a class effect of the T-type CCB, new calcium antagonists of this class have not been developed till lately. Recently, a clinical study examining the effect of efonidipine, which possesses potent activity on T-type as well as L-type calcium channels, on the development of heart failure is in progress, and is expected to demonstrate additional benefits of the T-type CCB [68]. This JATOS study group has released its tentative report that morbidity of 12 months treatment of efonidipine was 20.9/1,000, and its mortality was 1.7/1,000 [69], similar with morbidity of amlodipine treatment (VALUE: 33.4/1,000) or Nitrendipine treatment (Syst-Eur: 23.3/1,000, Syst-China:21.4/1,000) in clinical studies [5,6,40]. This study is in progress, and the positive outcome of the final report is expected.

As N-type channels are distributed along nerves, cilnidipine would affect the autonomic nervous system and subsequently decrease the blood pressure without inducing reflex tachycardia [70]. Cilnidipine improved the peripheral vascular resistance, mean blood pressure, atrial rate and increased the cardiac output in the chronic atrioventricular block dogs [8], and attenuated the incidences of ventricular premature beats during ischemia and reperfusion and decreased myocardial interstitial noradrenaline levels during ischemia and reperfusion in a rabbit model of myocardial infarction [71]. Recently, cilnidipine is reported to possess the blocking effect for T-type calcium current [72], and that effect may affect on the cilnidipine treatment.

In the clinical study, cilnidipine is demonstrated to suppress cardiac sympathetic overactivity in patients with essential hypertension [73]. Furthermore, Konda *et al.* [74] demonstrated that cilnidipine decreased mean blood pressure, and inhibited the changes in heart rate and plasma norepinephrine concentration induced by bilateral carotid artery occlusion in anesthetized dog. It also reduced myocardial interstitial noradrenaline levels and decreased the incidence of ventricular premature beats in rabbit myocardial infarction model [71]. Cilnidipine also reduces white coat effect in patients with essential hypertension [75]. Sakata *et al*. demonstrated that cilnidipine treatment improved the cardiac sympathetic overactivity of hypertension patients without changing plasma renin activity and plasma norepinephrine concentration, when amlodipine treatment did not change both of them by using 123I-metaiodo-benzylguanidine

(MIBG) cardiac imaging [73]. However, the effects of cilnidipine on cardiovascular events await large clinical trials.

3. CCBS AND ATHEROSCLEROSIS

A growing body of evidence has been accumulated that some of CCBs have anti-atherosclerotic action and/or possess antioxidant activity, both of which favor cardiovascular protection. Amlodipine and benidipine are demonstrated to prevent myocardial remodeling induced by chronic nitric oxide inhibition in rats [76]. Pretreatment of benidipine suppressed vascular cell adhesion molecule (VCAM) -1, intracellular cell adhesion molecule (ICAM) -1, and the induction of monocyte chemoattractant protein and interleukin-8 *in vitro* [77]. Roth *et al*. [78] demonstrated that amlodipine, felodipine, manidipine, verapamil, or diltiazem significantly decreased both the constitutive and platelet-derived growth factor β-dependent collagen deposition in the extracellular matrix formed by human vascular smooth muscle cells and fibroblasts. Finally, direct evaluation of the coronary artery with IVUS showed less progression of atherosclerosis in amlodipine-treated patients [46,79].

It has recently been demonstrated that T-type calcium channels are expressed in rat pulmonary microvascular endothelial cells, and mibefradil inhibits the calcium influx through these calcium channels [80]. Since T-type calcium current is induced by ischemia, it increases the intracellular calcium concentration and activates the nitric oxide synthesis [81]. Chronic treatment with mibefradil enhanced endothelium-dependent relaxations in arteries from Dahl salt sensitive rats with high salt diet [82]. Mibefradil, but not amlodipine or verapamil, is reported to inhibit the leukocyte adhesion [83]. Azelnidipine inhibited 8-iso-PGF2 alpha production, compared with nifedipine or amlodipine in cultured human arterial endothelial cells under hydrogen peroxide stimulation [84], and reduced tumor necrosis factor-α-induced interleukin-8 expression in endothelial cells [85]. Furthermore, Nomura *et al*. [86] reported that efonidipine improved platelet-derived microparticles, CD62P-, CD63-, PAC-1-, and annexin V-positive platelets, sICAM-1, sVCAM-1, sP-selectin, and sE-selectin levels in the hypertensive patients with diabetes. Thus, these studies suggest that novel CCBs can improve endothelial dysfunction and could be effective in the treatment of hypertension with diabetes.

4. CCBS AND CHRONIC KIDNEY DISEASES

Hypertension is one of the most important risk factors for the progression of renal disease [87,88]. In the follow-up study of the multiple risk factor intervention trial (MRFIT), a strong, graded relation between blood pressure and end-stage renal disease was identified [89]. Moreover, chronic renal dysfunction [90], proteinuria [42], and albuminuria [91,92] are independent risk factors of cerebrovascular and cardiovascular diseases. Thus, the treatment of hypertension constitutes a crucial strategy to minimize the development of renal disease and to reduce the risk of cardiovascular events. Among antihypertensive drugs, ACE inhibitors and ARB are the treatment of choice in patients with renal disease since proteinuria *per se* accelerates the renal dysfunction [93,94] and these classes of agents can reduce proteinuria [95,96]. In AASK study, the ability of amlodipine to retard the progression of renal disease is less than that of ramipril [97]. In the IDNT study, the risk of a doubling of the serum creatinine concentration and a relative risk of end-stage renal disease were lower in the irbesartan group than in the amlodipine group [98]. However, these studies do not suggest that the adverse effects of calcium antagonists on renal function. Furthermore, there is the possible renal protective action of the CCB. Several recent studies have demonstrated that long-acting nifedipine exerts beneficial action on the progression of renal injury [99]. Kumagai *et al*. [100] compared the effects of amlodipine and ACE inhibitors on the progression of renal disease in hypertensive patients with renal impairment, and demonstrated that increase in serum creatinine and creatinine clearance in amlodipine-treated group was comparable to that of ACE inhibitor-treated group during the one-year follow-up period. In the ALLHAT study, there

were no different relative risk of cardiovascular diseases and mortality among chlorthalidone, amlodipine, and lisinopril [41].

As CCBs are demonstrated to elicit predominant dilation of the afferent arteriole but less dilation of the efferent arteriole [101–106], the pressure overload to the glomerulus may result in glomerular hypertension and the subsequent glomerulosclerosis. It is well established that L-type calcium channels prevail on afferent arterioles whereas efferent arterioles lack functional activity of these channels. The segmental difference in the distribution of L-type calcium channels therefore would explain why CCBs cause predominant dilation of the afferent arteriole.

In contrast to predominant action of conventional types of CCBs on the afferent arteriole, several lines of studies have demonstrated that novel CCBs exert dilator action on both afferent and efferent arterioles (Fig. 1) [101–104,106]. Recently, some of CCBs has demonstrated to dilate both afferent and efferent arterioles. Because of lack of L-type calcium channels in the efferent arteriole, the dilatation of the efferent arteriole cannot be attributed to the class effect of the CCB. One of the possible mechanisms for the efferent arteriolar dilation by these CCBs is the blocking action on both L-type and other calcium channels, including T- and N-type calcium channels. It has recently been demonstrated that T-type calcium channels are present in both afferent and efferent arterioles of the rat kidney [107]. Ozawa *et al*. have demonstrated that mibefradil and nickel chloride dilate the angiotensin II-induced vasoconstriction of these arterioles [103].

Renal microvascular action of these CCBs could reduce glomerular capillary pressure and therefore ameliorate glomerular hypertension. Fujiwara *et al*. [108] demonstrated that efonidipine reduced proteinuria as little as ACEI and less than nifedipine in subtotal nephrectomised SHR, though blood pressure decrease was similar level among all of treatments. Hayashi *et al*. reported that efonidipine reduced proteinuria as much as ACE inhibitors, but caused less side-effects (cough and hyperkalemia) in hypertensive patients (Fig. 2) [109]. Furthermore, Zhou *et al*. [110] demonstrated that cilnidipine caused decreases in both afferent and efferent arteriolar resistance and ameliorated nephrosclerosis in l-NAME-treated SHR. Cilnidipine is also reported to reduce proteinuria in the hypertensive patients with renal sclerosis [111,112]. Collectively, these CCBs can possess renal protective action from the aspect of renal hemodynamics.

Although renal renin-angiotensin-aldosterone system plays an important role in mediating the physiological function, this system also participates in the pathological process of the development of renal injury. Both ACE inhibitors and ARB effectively reduce proteinuria independently of blood pressure, and the inhibition of renin-angiotensin system is known to retard the progression of renal dysfunction. Recent investigations suggest that local renin-angiotensin system is enhanced apart from systemic renin-angiotensin system. Kobori *et al*. [113–115] have demonstrated that enhanced local renal renin-angiotensin system constitutes an important factor for the acceleration of hypertensive nephropathy. Furthermore, evidence has accrued that aldosterone is associated with the increased event of heart failure [116] and induce renal injury independently [117] from renin-angiotensin system. Nifedipine is known to reduce aldosterone selection [118], and mibefradil also reduced renin secretion [119]. Rossier *et al*. [120] demonstrated that aldosterone secretion appears to be related to T-type channel activity compared with L-type channel activity during activation of bovine adrenal glomerulosa cells. Arima *et al*. [121] also demonstrated that aldosterone elicited constriction of both afferent and efferent arterioles, and efonidipine reversed this response in the isolated renal microvessels *in vitro*. In this regards, dual L- and T-type CCB may retard the progression of renal dysfunction by blocking renin-angiotensin-aldosterone system.

CONCLUSION

More than 40 years have passed since the development of the CCB, and several classes of CCBs are in clinical use for the treatment of hypertension because of potent vasodepressor action. Although CCBs, particularly with short acting nature, were deemed as drugs causing cardiovascular events, subsequent studies using long-acting CCBs clearly demonstrate benefits from these agents in the field of cardiovascular and kidney disease. A growing body of studies now reveals that a number of recently-developed CCBs exert inhibitory action on multiple calcium channel subtypes, including L-, T- and N-type channels. Since these channels have been demonstrated to be distributed widely and have substantial effect on cardiovascular and neurohumoral systems, dual or triple blockade of calcium channels may offer additional benefits as a therapeutic strategy of hypertension (Table 2).

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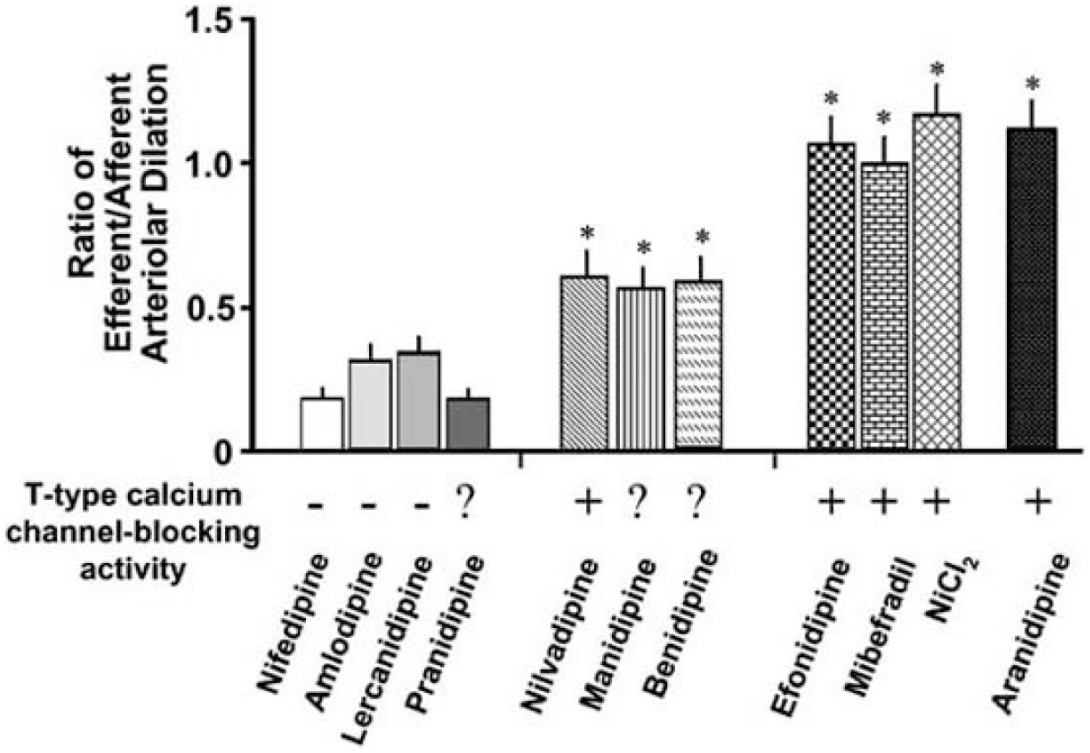

Fig. 1.

Divergent vasodilator action of calcium antagonists on efferent arterioles. Based on the relative activity on efferent *vs*. afferent arterioles, calcium antagonists are classified into 3 groups. The first group of calcium antagonists (e.g., nifedipine) elicits predominant vasodilation of afferent arterioles, with modest action on efferent and efferent arterioles. The second group (e.g., nilvadipine) produces both afferent and efferent arteriolar vasodilation, although the efferent arteriolar vasodilation is less than that on the afferent arteriole. The third group of calcium antagonists (e.g., efonidipine) potently relaxes both afferent and efferent arterioles, with nearly the same activity on these vessels. *$p < 0.05$ *vs*. baseline. ? = Not examined. From Hayashi *et al*. [106] with modifications.

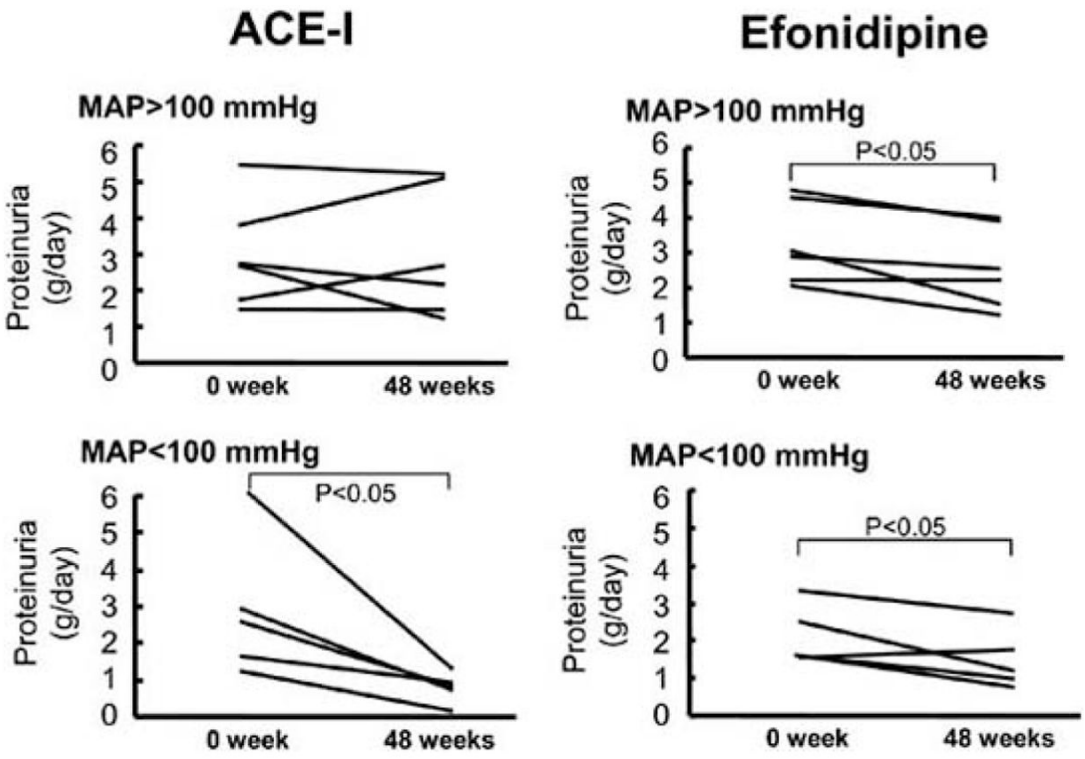

Fig. 2.
Role of systemic blood pressure in the development of proteinuria in patients with proteinuria > 1 g/day treated with angiotensin converting enzyme inhibitors and efonidipine. ACE-I = angiotensin converting enzyme inhibitors; MAP = mean arterial pressure. From Hayashi *et al*. [109] with modifications.

Table 1

Pharmacology and Distribution of Calcium Channels

Current	α_1 subunit	Channel	Distribution	Inhibitors
P	α_{1A}	$Ca_V2.1$	neurons	ω-agatoxin IVA
Q	α_{1A}	$Ca_V2.1$	neurons	ω-agatoxin IVA
N	α_{1B}	$Ca_V2.2$	neurons	ω-conotoxin GIVA
R	α_{1E}	$Ca_V2.3$	neurons	SNX-482
L	α_{1S}	$Ca_V1.1$	skeletal muscle	DHP/PAA/BZP
	α_{1C}	$Ca_V1.2$	heart, endocrine, neurons	DHP/PAA/BZP
	α_{1D}	$Ca_V1.3$	endocrine, neurons	DHP/PAA/BZP
	α_{1F}	$Ca_V1.4$	retina	N/A
T	α_{1G}	$Ca_V3.1$	neurons, heart	N/A
	α_{1H}	$Ca_V3.2$	neurons, heart	N/A
	α_{1I}	$Ca_V3.3$	neurons	N/A

DHP: dihydropyridines, PAA: phenylalkylamines, BZP: benzothiazepines

From Triggle [13] with modifications

Table 2

Benefits and Defects of CCBs

CCBs	Benefits	Defects
Short acting	Prompt, Reliable	Too Sharp
Long acting	Mild, Continuous	Taking Long Time to Get Stable Actions
L-type selective	Prompt Antihypertensive Action	(not yet reported)
L- & T-type	Chronotropic, Inotropic, and Renoprotective Effects	(not yet reported)
L- & N-type	Direct Action on Autonomic Nerves	(not yet reported)