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# Dual L/N-Type Ca<sup>2+</sup> Channel Blocker: Cilnidipine as a New Type of Antihypertensive Drug

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## 1. Introduction

Cilnidipine is a unique dihydropyridine derivative Ca<sup>2+</sup> channel blocker with an inhibitory action on the sympathetic N-type Ca<sup>2+</sup> channels (Uneyama et al., 1999a). It has been clarified that cilnidipine exerts antisympathetic actions in various examinations from cell to human levels. Furthermore, its renoprotective, neuroprotective and cardioprotective effects have been demonstrated in clinical practice or animal examinations. After the introduction of nifedipine, many Ca<sup>2+</sup> channel blockers with long-lasting action have been synthesized to decline sympathetic reflex during antihypertensive therapy. Based on each pharmacokinetic profile, Ca<sup>2+</sup> channel blockers have been divided into three groups; namely, 1st, 2nd, and 3rd generation. Since cilnidipine directly inhibits the sympathetic neurotransmitter release by N-type Ca<sup>2+</sup> channel-blocking property, the drug can be expected as 4th generation, providing an effective strategy for the treatment of cardiovascular diseases (Takahara, 2009).

Recently, cilnidipine has been demonstrated to suppress renin-angiotensin-aldosterone system at anti-hypertensive doses in animal examinations, whereas other Ca<sup>2+</sup> channel blockers usually activates such vasopressor system after acute or repeated administrations. Interestingly, antihypertensive therapies with angiotensin II receptor blockers sometimes activate renin-angiotensin system, which is effectively suppressed by cilnidipine. This may provide synergistic and effective therapeutic strategies during combined administration of cilnidipine and angiotensin II receptor blockers. The possible mechanisms to suppress renin-angiotensin-aldosterone system appear to be clarified. In human adrenocortical cells, where N-type Ca<sup>2+</sup> channels are recently found to act as a source of intracellular Ca<sup>2+</sup> mobilization, cilnidipine as well as a specific N-type Ca<sup>2+</sup> channel blocker  $\omega$ -conotoxin effectively inhibits angiotensin II-induced aldosterone synthesis.

In this chapter, we introduce a pharmacological profile of cilnidipine in combined with its clinical antihypertensive and anti-sympathetic actions. We further review utilities of cilnidipine for management of hypertension and its complications through inhibition of sympathetic N-type Ca<sup>2+</sup> channels and renin-angiotensin-aldosterone system.

## 2. Ca<sup>2+</sup> channels: Physiological role and pharmacological modification

Rise in intracellular Ca<sup>2+</sup> triggers a variety of physiological processes, and there are many channels and pumps involved in controlling intracellular Ca<sup>2+</sup> level. Among them, voltage-

gated  $\text{Ca}^{2+}$  channels play a key role in this process, which is a pharmacological target molecule for so-called  $\text{Ca}^{2+}$  channel blockers. In excitatory cells such as smooth and cardiac muscle cells and neurons, high voltage-activated (HVA)  $\text{Ca}^{2+}$  channels are well known to regulate a variety of cellular events, which include muscle contraction, neuronal electrical activity, the release of neurotransmitters and hormones as well as gene expressions. On the other hand, low voltage-activated (LVA)  $\text{Ca}^{2+}$  channels are expressed throughout the body, including nervous tissue, heart, kidney, smooth muscle and many endocrine organs. The channels in the brain are considered to be involved in repetitive low threshold firing and nociception. In the heart, they are expressed in the sino-atrial node and are considered to participate in cardiac pacemaking (Tanaka & Shigenobu, 2005).

### 2.1 Classification of $\text{Ca}^{2+}$ channels

$\text{Ca}^{2+}$  channels are classified into at least 6 subtypes; namely, L-, N-, P-, Q-, R-, and T-type, based on electrophysiological and pharmacological evidences (Varadi et al., 1995). The T-type  $\text{Ca}^{2+}$  channels are known as low-voltage-activated  $\text{Ca}^{2+}$  channels that activate and deactivate slowly, but inactivate rapidly. The other five types of  $\text{Ca}^{2+}$  channels are all high-voltage-activated  $\text{Ca}^{2+}$  channels, which depolarize at approximately  $-40$  mV. Molecular biological techniques have shown that  $\text{Ca}^{2+}$  channels are composed of  $\alpha_1$ ,  $\alpha_2$ - $\delta$ ,  $\beta$ , and  $\gamma$  subunits using L-type  $\text{Ca}^{2+}$  channels from skeletal muscles. In particular, the  $\alpha_1$  subunit forms the  $\text{Ca}^{2+}$  transmission pore, which fulfills the most important function. Furthermore, 10  $\alpha_1$  subunits have been cloned and classified into 3 subfamilies: Cav1.x; Cav2.x; and Cav3.x, based on their gene sequence similarity (Catterall et al., 2003). More importantly, the  $\alpha_1$  subunit has a binding site for  $\text{Ca}^{2+}$  channel blockers.

### 2.2 $\text{Ca}^{2+}$ channels in the cardiovascular system

In the cardiovascular system, L-type  $\text{Ca}^{2+}$  channels are predominantly expressed in the heart and vessels, which regulate cardiac contractility, sinus nodal function and vascular tone.  $\beta$ -adrenergic stimulation enhances the force of cardiac contraction through activation of cAMP-mediated activation of protein kinase A that in turn increases the L-type  $\text{Ca}^{2+}$  channel currents, causing a greater rate of release of  $\text{Ca}^{2+}$  from the sarcoplasmic reticulum. In the arterial vessels, receptor stimulation or membrane depolarization activates  $\text{Ca}^{2+}$  influx through  $\text{Ca}^{2+}$  channels and myosin light chain kinase, leading to smooth muscle contraction. Thus, L-type  $\text{Ca}^{2+}$  channels have been recognized as a pharmacological target for the treatment of cardiovascular disease. Most of  $\text{Ca}^{2+}$  channel blockers are well known to have selectivity for vascular tissues rather than cardiac function. On the other hand, verapamil, diltiazem and bepridil have been shown to possess less vascular selectivity, which are used for supraventricular and/or ventricular arrhythmias. The selectivity of  $\text{Ca}^{2+}$  channel blockers for cardiac and vascular actions may be associated with that the membrane potential in vascular smooth muscle cells is definitely less negative than the diastolic membrane potential of working cardiac muscle cells. In the vascular system, arterioles appear to be more sensitive to  $\text{Ca}^{2+}$  channel blockers than venules; orthostatic hypotension is not a common adverse effect.

### 2.3 $\text{Ca}^{2+}$ channels in the sympathetic nerve system

The most thoroughly characterized role of  $\text{Ca}^{2+}$  in the nerve is the triggering of exocytosis. The synaptic vesicle cycles at nerve endings could be divided into the following processes:

a) translocation of the synaptic vesicle filled with norepinephrine and epinephrine to the active zone; b) docking at the active zone and priming; c) fusion triggered by Ca<sup>2+</sup> and exocytosis; d) endocytosis of empty synaptic vesicle to become coated vesicles; e) endosome fusion and budding to make the synaptic vesicle re-generation; and f) the neurotransmitters uptake to the regenerated synaptic vesicle. Entered Ca<sup>2+</sup> through voltage-gated Ca<sup>2+</sup> channels bind to synaptotagmin, changing the conformation of a large protein superfamily called as SNARE complexes (formed by 4  $\alpha$ -helices; synaptobrevin, synaptotagmin, syntaxin and SNAP 25), leading to fusion of vesicle membrane into plasma membrane. At these steps, the N-type Ca<sup>2+</sup> channel plays an important role as a Ca<sup>2+</sup> supplier. More than 60 Ca<sup>2+</sup> channels open for each vesicle for rapid release (Uneyama et al., 1999).

In the sympathetic nervous systems, N-type Ca<sup>2+</sup> channels are localized at the nerve endings. Using a patch clamp method, N-type Ca<sup>2+</sup> channels are shown to contribute about 85% of all other types of Ca<sup>2+</sup> channels in the sympathetic neuronal cells. N-type Ca<sup>2+</sup> channels have been demonstrated to predominantly regulate norepinephrine release in the superior cervical ganglia neurons using a selective N-type Ca<sup>2+</sup> channel blocker  $\omega$ -conotoxin GVIA (Hirning et al., 1988). This finding was further supported by subsequent experiments using isolated rat arterial preparations. In a clinical study, systemic administration of  $\omega$ -conotoxin MVIIA (SNX-111) has been shown to induce sympatholytic action.

#### 2.4 Ca<sup>2+</sup> channels in the adrenal gland

Chromaffin cells in the medulla of the adrenal gland are innervated by the splanchnic nerve and secrete catecholamines into the blood stream. In anesthetized dogs, the splanchnic nerve stimulation increased the catecholamine secretion from adrenal gland, which was effectively inhibited by an N-type Ca<sup>2+</sup> channel blocker  $\omega$ -conotoxin GVIA but not by L-type Ca<sup>2+</sup> channel blockers nifedipine or verapamil (Kimura et al., 1994). Many in vitro studies also support that N-type Ca<sup>2+</sup> channels are localized at chromaffin cells to regulate the release of catecholamine. Recently, it is shown that N-type Ca<sup>2+</sup> channels are also localized at the human adrenocortical cells, playing an important role in the secretion of adrenocortical hormones (Aritomi et al., 2011a). Furthermore, N-type Ca<sup>2+</sup> channels may offer the different way of controlling corticosteroid production in adrenocortical cells than other types of voltage-gated Ca<sup>2+</sup> channels.

### 3. New generation Ca<sup>2+</sup> channel blocker: Cilnidipine

Cilnidipine is a unique dihydropyridine derivative L-type Ca<sup>2+</sup> channel blocker with an inhibitory action on the sympathetic N-type Ca<sup>2+</sup> channels. As shown in Fig. 1, Ca<sup>2+</sup> channels are ordinarily activated by membrane depolarization in the vascular cells or sympathetic neurons, leading to vascular contraction or neurotransmitter releases. During antihypertensive therapies with pure L-type Ca<sup>2+</sup> channel blockers like nifedipine, the sympathetic reflex is sometimes occurred due to hypotension, leading to activation of sympathetic N-type Ca<sup>2+</sup> channels, which induces several cardiovascular responses including vascular contraction, tachycardia and renin secretion (Takahara 2009). Cilnidipine can directly inhibit the sympathetic neurotransmitter release by its N-type Ca<sup>2+</sup> channel-blocking property, which may reduce risk of cardiovascular diseases closely associated with sympathetic nerve activation. The wide variety of pharmacological actions of cilnidipine has been investigated, which is summarized in Table 1.

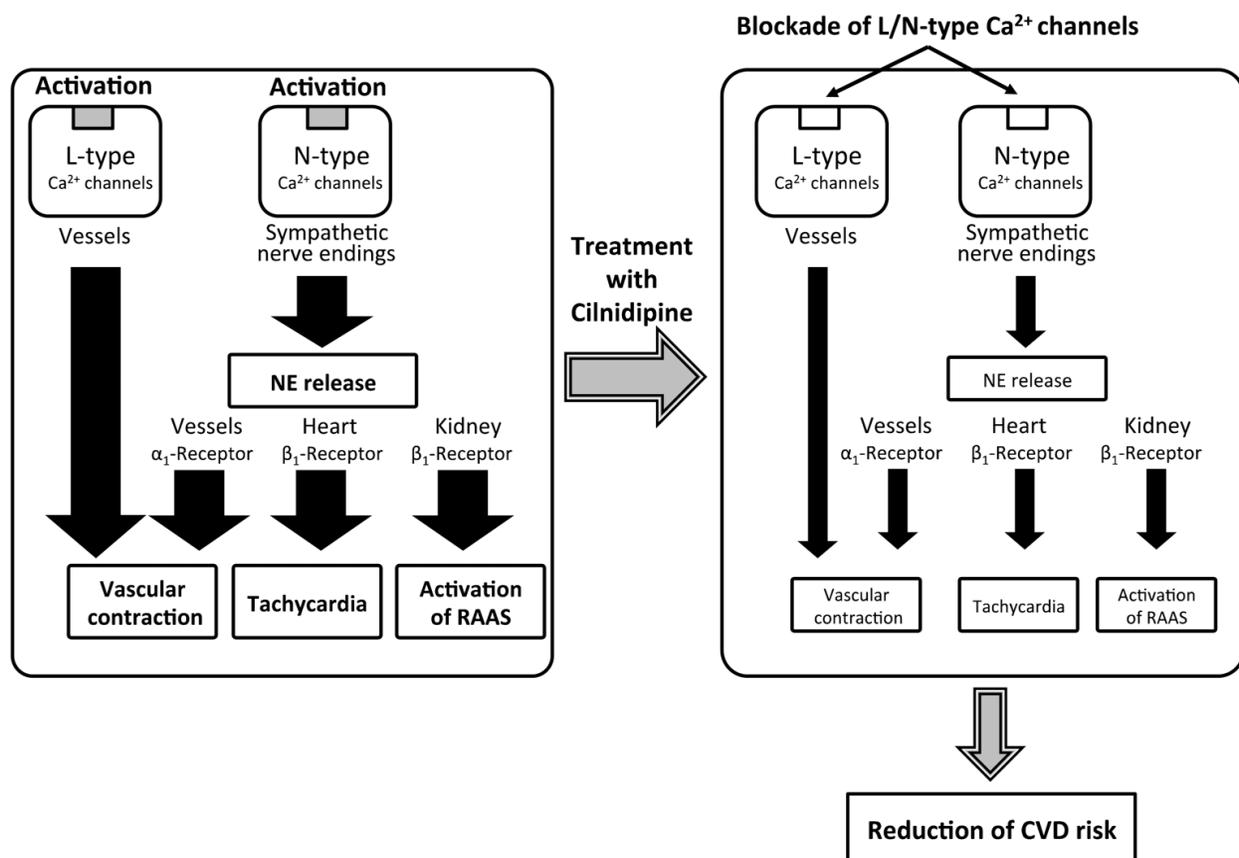


Fig. 1. Diagrammatic representation of L/N-type dual action of cilnidipine. Cilnidipine directly inhibits the sympathetic neurotransmitter (norepinephrine; NE) release by N-type Ca<sup>2+</sup> channel-blocking property in addition to vascular L-type Ca<sup>2+</sup> channel inhibition, leading to suppression of renin-angiotensin-aldosterone system (RAAS). Thus, the drug can be expected to provide an effective strategy for the treatment of cardiovascular diseases (CVD).

### 3.1 Pharmacology

L-type Ca<sup>2+</sup> channel-blocking actions of cilnidipine were widely examined in earlier experimental studies, showing that its potency was greater than that of nifedipine. In 1997, N-type Ca<sup>2+</sup> channel-blocking action was found in cilnidipine (Uneyama et al., 1997). Submicromolecular concentrations of cilnidipine effectively suppressed N-type Ca<sup>2+</sup> channel currents in isolated sympathetic neurons. The inhibitory effect of various dihydropyridines on cardiac L-type Ca<sup>2+</sup> channels was further compared in isolated ventricular myocytes with that on N-type Ca<sup>2+</sup> channels in superior cervical ganglion neurons of the rat (Uneyama et al., 1999b). In that study, all dihydropyridines, except cilnidipine, showed a small inhibitory effect at a concentration of 1 μM. The N-type channel-blocking action of cilnidipine has also been confirmed in IMR-32 human neuroblastoma cells and PC12 pheochromocytoma of the rat adrenal medulla cells. Furthermore, it has been demonstrated that the N-type Ca<sup>2+</sup> channel-blocking effects of cilnidipine leading to anti-sympathetic action can be observed at its anti-hypertensive doses (Takahara et al., 2002).

Mode of action	Inhibition of L-type Ca <sup>2+</sup> channels (vascular smooth muscle, in vitro); inhibition of N-type Ca <sup>2+</sup> channels (sympathetic neuron, in vitro)
Pharmacology	
1) Cardiovascular action	Vascular relaxation (in vitro); hypotensive action (in vivo)
2) Anti-sympathetic action	Decrease of catecholamine release, tissue (kidney) norepinephrine level, (in vitro, in vivo); inhibition of sympathetic tachycardia and cold stress-induced vasoconstriction (in vivo); decrease in plasma/urinary norepinephrine, muscle sympathetic nerve activity, low frequency/high frequency ratio (LF/HF ratio), and plasma level of $\beta$ -thromboglobulin (clinical)
3) Suppression of renin-angiotensin-aldosterone system	Decrease in plasma level of angiotensin II and aldosterone (in vivo, clinical); inhibition of aldosterone production (adrenocortical cells, in vitro); inhibition of reflex aldosterone production, and angiotensin II-renin feedback (in vivo)
4) Anti-oxidation	Inhibition of NADPH oxidase-derived superoxide production (kidney, in vivo)
5) Others	Improvement of insulin resistance (in vivo); increases of nitric oxide production (in vitro); protection from retinal neuronal injury (in vivo); anti-nociception (in vivo)
Antihypertensive action	
1) Animal model	Antihypertensive action in spontaneously hypertensive rats, stroke-prone spontaneously hypertensive rat, renal hypertensive rats, DOCA-salt hypertensive rats, Otsuka Long-Evans Tokushima Fatty rat, Dahl salt sensitive rat and 2-kidney 1-clip hypertensive dogs (in vivo)
2) Human	Essential hypertension; severe hypertension; hypertension with chronic kidney disease, cerebrovascular disease or diabetes (clinical)
Actions in key organs	
1) Kidney	Increase in renal blood flow; dilation of afferent and efferent arterioles; natriuresis; inhibition of renal nerve stimulation-induced antinatriuresis; suppression of albuminuria; glomerular hypertrophy and interstitial fibrosis; decrease in renal angiotensin II content (in vivo); decrease in albuminuria and urinary protein (clinical)
2) Heart	Increase in coronary blood flow (in vitro, in vivo); suppression of vasopressin-induced ST depression; reduction of the myocardial infarct size and incidence of ventricular premature beats after ischemia-reperfusion; abbreviation of abnormally prolonged ventricular repolarization (in vivo); decrease in BNP, LV mass index, heart rate and cardiothoracic ratio (clinical)
3) Brain	Downward shift of the lower limit of autoregulation for cerebral blood flow; reduction of the cerebral infarction size (in vivo); increase in cerebral blood flow (clinical)

Table 1. Summary of pharmacological effects of cilnidipine

### 3.2 Antihypertensive action

In animal examinations, cilnidipine has a slow-onset and long-lasting antihypertensive action in spontaneously hypertensive rats, renal hypertensive rats, DOCA-salt hypertensive rats, and 2-kidney 1-clip hypertensive dogs. In addition, cilnidipine significantly decreases the blood pressure of stroke-prone spontaneously hypertensive rats (Watanabe et al. 1995a) and Dahl salt-sensitive rats (Aritomi et al., 2010).

In clinical studies, the antihypertensive effect of cilnidipine has been demonstrated in hypertensive patients, and also in patients with severe hypertension or with complications such as chronic kidney disease, cerebrovascular disease and diabetes. Cilnidipine has been reported to improve some hypertensive conditions closely associated with sympathetic nerve activation such as morning hypertension, nocturnal hypertension, white-coat phenomenon, mental stress and cold stress (Yamagishi, 2006).

### 3.3 Anti-sympathetic action

The anti-sympathetic action of cilnidipine has been demonstrated in several experimental studies; increases in the heart rate and plasma catecholamine level induced by cold stress, hypotension or spinal nerve stimulation of the rat were effectively suppressed by cilnidipine but not other  $\text{Ca}^{2+}$  channel blockers (Uneyama et al., 1999a). Importantly, the N-type  $\text{Ca}^{2+}$  channel-blockade hardly affects parasympathetic neurotransmission (Konda et al., 2001). We compared effects of 4  $\text{Ca}^{2+}$  channel blockers (nifedipine, amlodipine, azelnidipine and cilnidipine) on hypotension-induced sympathetic activation in the halothane-anesthetized canine model (Fig. 2, Takahara et al., 2007; Ishizaka et al., 2010). Intravenous infusion of nifedipine or amlodipine decreased the mean blood pressure with increments of heart rate and cardiac contractility. Azelnidipine also decreased the mean blood pressure with an increment of cardiac contractility whereas marked tachycardia was not induced, which is in accordance with a previous report showing its direct suppressive effects on sinus nodal automaticity. On the other hand, no significant change in the heart rate or cardiac contractility was observed after intravenous infusion of cilnidipine. These results strongly indicate that cilnidipine is desirable among  $\text{Ca}^{2+}$  channel blockers to minimize reflex sympathetic nerve activation.

Similar actions of cilnidipine can be observed in the clinical investigations using a parameter of plasma/urinary norepinephrine,  $^{123}\text{I}$ -metaiodobenzylguanidine (MIBG), muscle sympathetic nerve activity, low frequency/high frequency ratio (LF/HF ratio) or heart rate, each of which help us better understand their clinical effects on sympathetic nerve activity (Takahara 2009). More importantly, a clinical study of cold pressor test has shown that cilnidipine decreased plasma level of  $\beta$ -thromboglobulin, a marker of platelet activation, which may prevent arterial thrombosis formation associated with increased sympathetic tone.

### 3.4 Renal action

There are observations that L-type  $\text{Ca}^{2+}$  channel blockers, such as verapamil, nifedipine, felodipine and nifedipine, induce renal vasodilation and natriuresis in anesthetized dogs and rats. Similarly, cilnidipine increases the renal blood flow and urinary  $\text{Na}^+$  excretion without affecting creatinine clearance in dogs (Takahara et al., 1997). The kidney is densely innervated by adrenergic nerve fibers. The renal nerve stimulation releases norepinephrine

and induces renal vasoconstriction, anti-natriuresis and renin secretion via activation of adrenoceptors in the vascular vessels, renal tubular cells and granular cells of the juxtaglomerular apparatus, respectively, which cannot be suppressed by typical L-type Ca<sup>2+</sup> channel blockers in several experimental studies (Ogasawara et al., 1993). On the other hand, it has been demonstrated that these responses to renal nerve stimulation are suppressed by natriuretic doses of cilnidipine via its N-type Ca<sup>2+</sup> channel blocking property.

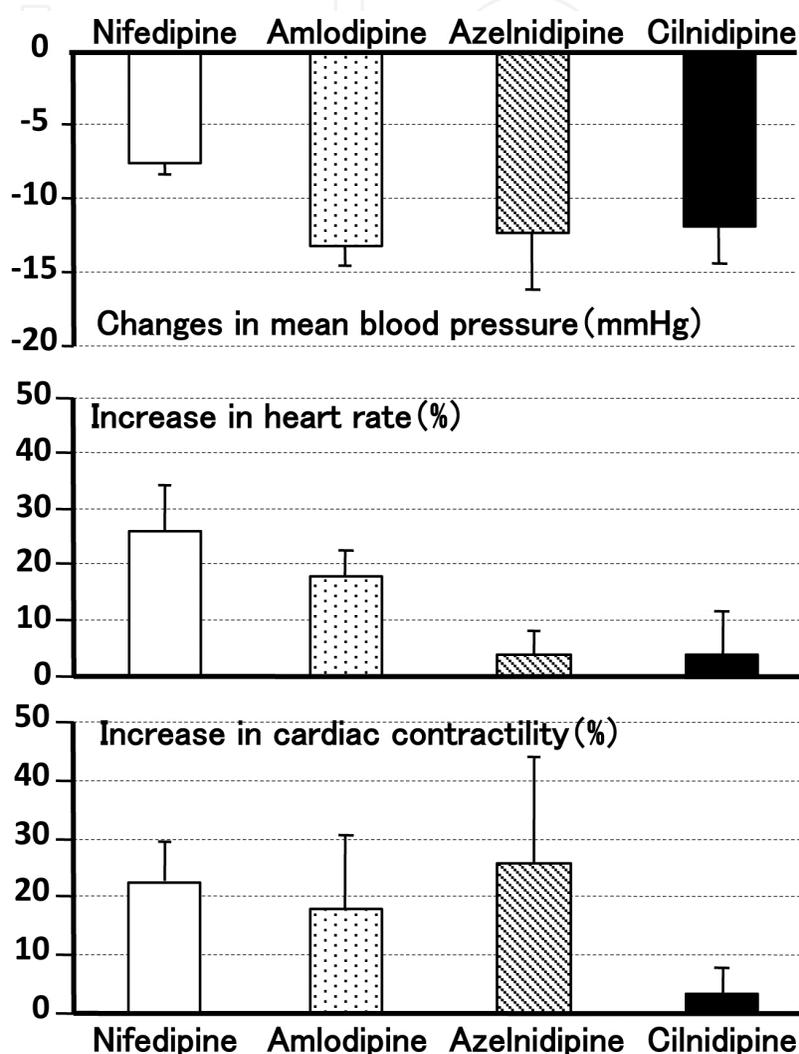


Fig. 2. Comparison of effects of Ca<sup>2+</sup> channel blockers on hypotension-induced sympathetic activation. Nifedipine, amlodipine, azelnidipine or cilnidipine was intravenously administered to halothane-anesthetized dogs, and changes in mean blood pressure, heart rate and cardiac contractility were observed. The intravenous doses of nifedipine, amlodipine, azelnidipine and cilnidipine used were 3, 200, 70 and 3  $\mu\text{g}/\text{kg}$ , respectively. Values are expressed as means  $\pm$  SE. Data are quoted and modified from Takahara et al., 2007 and Ishizaka et al., 2010.

Glomerular filtration is essentially regulated by afferent and efferent arterial tone. Since sensitivity of Ca<sup>2+</sup> channel blockers to afferent and efferent arteries varies, Ca<sup>2+</sup> channel blockers should be appropriately selected for hypertensive patients with chronic kidney disease. Since the sympathetic nerves are distributed to the afferent and efferent arteries, N-

type Ca<sup>2+</sup> channel-blocking activity may be partly associated with control of the glomerular pressure. Indeed, cilnidipine has been demonstrated to dilate both afferent and efferent arteries using the hydronephrotic kidney model of the rat (Konno & Kimura, 2008). Furthermore, in renal injury animal models, cilnidipine reduces glomerular capillary pressure, afferent and efferent arteriolar resistances, urinary albumin excretion, and glomerular volume as well as plasma norepinephrine levels.

In clinical studies, cilnidipine significantly decreased urinary albumin excretion without affecting serum creatinine concentration in hypertensive patients, which is comparable to the angiotensin-converting enzyme inhibitor benazepril. Other studies have shown that the renal protective effect of cilnidipine was greater than that of pure L-type Ca<sup>2+</sup> channel blockers. Furthermore, the combination of cilnidipine and valsartan was shown to decrease the albumin/creatinine ratio more markedly than valsartan alone. Recently, the multi-center, open-labeled and randomized trial of Cilnidipine versus Amlodipine Randomized Trial for Evaluation in Renal disease (CARTER) has shown that cilnidipine is superior to amlodipine in preventing the progression of proteinuria in patients with hypertension and chronic renal disease when coupled with a renin-angiotensin system inhibitor (Fujita et al., 2007).

### 3.5 Cardiovascular action

Since the first generation of Ca<sup>2+</sup> channel blockers were known to suppress cardiac functions such as contractility, sino-atrial automaticity, and atrioventricular conduction at vasodilator doses, pharmaceutical companies have developed new Ca<sup>2+</sup> channel blockers with higher vascular selectivity in addition to slow kinetics as a new generation. The blood-perfused canine heart preparation is an excellent model to quantitatively determine cardio-vascular selectivity of Ca<sup>2+</sup> channel blockers, and many Ca<sup>2+</sup> channel blockers were analyzed using this model (Taira, 1987). Cilnidipine has about 10 times more potent coronary vasodilator action and higher vascular selectivity than nifedipine in this heart preparation. An *in vivo* experimental study has confirmed that cilnidipine shows anti-anginal effects in the vasopressin-induced angina model (Saitoh et al., 2003). A recent study indicates that cilnidipine relaxes human arteries through Ca<sup>2+</sup> channel antagonism and increases production of nitric oxide by enhancement of endothelial nitric oxide synthase in the human internal thoracic artery (Fan et al., 2011).

The cardioprotective action of cilnidipine against ischemia has been analyzed in a rabbit model of myocardial infarction, in which cilnidipine decreased the myocardial interstitial norepinephrine levels during ischemia and reperfusion periods, leading to reduction of the myocardial infarct size and incidence of ventricular premature beats (Nagai et al., 2005). Clinically, cilnidipine has been reported to improve left ventricular diastolic function in patients with hypertensive heart disease (Kosaka et al., 2009). These cardioprotective actions are probably associated with suppression of cardiac sympathetic overactivity via blockade of N-type Ca<sup>2+</sup> channels and/or anti-oxidative (as described below) effects of cilnidipine, which should be further clarified.

### 3.6 Cerebrovascular action

The brain is known to have an autoregulatory capacity that allows cerebral blood vessels to maintain constant cerebral blood flow by dilating or contracting in response to abrupt

changes in blood pressure. It is demonstrated that the cerebral blood flow was maintained regardless of whether blood pressure was decreased by cilnidipine. Furthermore, cilnidipine had the activity to shift downward the lower limit of autoregulation for cerebral blood flow according to the results of the estimation of the lower limit of autoregulation for cerebral blood flow by exsanguination (Watanabe et al., 1995b). Interestingly, an antihypertensive and anti-sympathetic dose of cilnidipine reduced the size of cerebral infarction in the rat focal brain ischemia model in contrast to nilvadipine (Takahara et al., 2004), which is in accordance with previous study using a peptidic N-type Ca<sup>2+</sup> channel blocker  $\omega$ -conotoxin MVIIA. Thus, the results may support that N-type Ca<sup>2+</sup> channel activation includes pathophysiological process of brain ischemia.

### 3.7 Metabolic syndrome

Pancreatic insulin secretion from  $\beta$ -cells and glucagon secretion from  $\alpha$ -cells in the islets of Langerhans are Ca<sup>2+</sup>-dependent processes initiated by Ca<sup>2+</sup> influx probably through N-type Ca<sup>2+</sup> channels. In a study using N-type Ca<sup>2+</sup> channel  $\alpha_{1B}$ -subunit-deficient homozygous knockout mice fed normal diet, there was improved glucose tolerance without any change in insulin sensitivity, and also body weight gain reduced in the mice fed a high-fat diet (Takahashi et al., 2005). In another study with fructose-fed rats, insulin sensitivity was significantly lower than in controls, and insulin resistance improved significantly after cilnidipine treatment (Takada et al., 2001). These imply that N-type Ca<sup>2+</sup> channels play a significant role in glucose homeostasis.

Clinically, it was revealed that cilnidipine significantly reduced 24-hour urinary catecholamines in hypertensive patients with type 2 diabetes, and thereby may improve insulin resistance (Takeda et al., 1999). Also, it is demonstrated that with cilnidipine treatment in patients with obesity, fasting serum immunoreactive insulin (F-IRI) and insulin resistance index as assessed by homeostasis model assessment (HOMA-R) lowered, and serum dehydroepiandrosterone (DHEA) and serum DHEA-sulfate (DHEA-S) increased (Ueshiba & Miyachi, 2002).

## 4. Pleiotropic effects of cilnidipine

Renoprotective, neuroprotective and cardioprotective effects of cilnidipine have been demonstrated in clinical practice or animal examinations. It is noticed that cilnidipine may have pleiotropic effects besides N-type Ca<sup>2+</sup> channel-blocking action.

### 4.1 Anti-oxidation

Dihydropyridine derivatives including nifedipine have been reported to act as lipophilic chain-breaking antioxidants; however, there are larger differences in their lipophilicity among dihydropyridines. Lipophilicity of cilnidipine is greater than that of amlodipine, which implies that cilnidipine itself can reduce oxidative stress independently in addition to its N-type Ca<sup>2+</sup> channel blockade action.

Excess reactive oxygen species play an essential role in the development of a variety of renal diseases such as glomerulonephritis and tubulointerstitial nephritis. Indeed, in the kidney, cilnidipine significantly inhibited the increase in NADPH oxidase-derived superoxide

production, whereas amlodipine had no effect on the activation of NADPH oxidase in the deoxycorticosterone acetate-salt rat (Toba et al., 2011). Also, cilnidipine elicits podocyte-protection and anti-proteinuric effect in SHR/ND mcr-cp rat model of spontaneous hypertension through the reduction of renal AngII level and a subsequent reduction in oxidative stress (Fan et al., 2010). N-type  $\text{Ca}^{2+}$  channels localized in podocyte have been shown to play an important role in angiotensin II-induced superoxide production, which may partly explain the renoprotective mechanisms of cilnidipine. Antiproteinuric effect of cilnidipine in the CARTER study (Fujita et al., 2007) is in part explained by its superior antioxidant activity.

In addition, cilnidipine shows neuroprotection in the model of oxidative stress-induced neurotoxicity using PC12 cells (Lee et al., 2009), which may partly explain the mechanisms of cilnidipine that reduced infarction volume in the rat focal brain ischemia model.

#### 4.2 Suppression of renin-angiotensin-aldosterone system

It is widely known that renin secretion from the juxtaglomerular apparatus is closely associated with renal sympathetic nerve activity. Thus, cilnidipine may alter renin-angiotensin-aldosterone system. In recent studies using spontaneously hypertensive rats, whereas an L-type  $\text{Ca}^{2+}$  channel blocker amlodipine increased plasma renin activity and angiotensin II levels at antihypertensive doses, cilnidipine failed to affect plasma renin activity or plasma norepinephrine and angiotensin II levels, which strongly supports that cilnidipine suppresses renin-angiotensin system through sympathetic N-type  $\text{Ca}^{2+}$  channel blockade (Konda et al., 2009). In a previous study using the canine cardiac sudden death model, it was found for the first time that cilnidipine decreased the plasma concentration aldosterone level (Takahara et al., 2009). The curious action of cilnidipine was also confirmed in hypertensive rats. A recent study has clearly demonstrated that the endocrine mechanisms of angiotensin II-induced aldosterone production in the adrenocortical cells are closely associated with activities of N-type  $\text{Ca}^{2+}$  channels (Aritomi et al., 2011a).

Antihypertensive therapies with angiotensin II receptor blockers sometimes activate renin-angiotensin system. As shown in Fig. 3, increases in plasma renin activity and plasma angiotensin II levels can be observed by oral administration of valsartan in spontaneously hypertensive rats, which were effectively suppressed by cilnidipine but not by amlodipine (Aritomi et al., 2011b). Thus, cilnidipine is expected to provide synergistic and effective therapeutic strategies when administered with angiotensin II receptor blockers.

#### 4.3 Abbreviation of prolonged QT-interval

The heart of canine chronic atrioventricular block model (cardiac sudden death model) is known to have a ventricular electrical remodeling, which mimics the pathophysiology of long QT syndrome (Sugiyama, 2008). Using this model, we explored a new pharmacological therapeutic strategy for prevention of cardiac sudden death (Fig. 4; Takahara et al., 2009). Amlodipine, cilnidipine or an angiotensin II receptor blocker candesartan was orally administered to the dogs for 4 weeks. Amlodipine and cilnidipine decreased the blood pressure, while candesartan hardly affected it. The QT interval and monophasic action potential duration were shortened only in the cilnidipine group, but such effects were not observed in the amlodipine or candesartan group. Plasma concentrations of angiotensin II

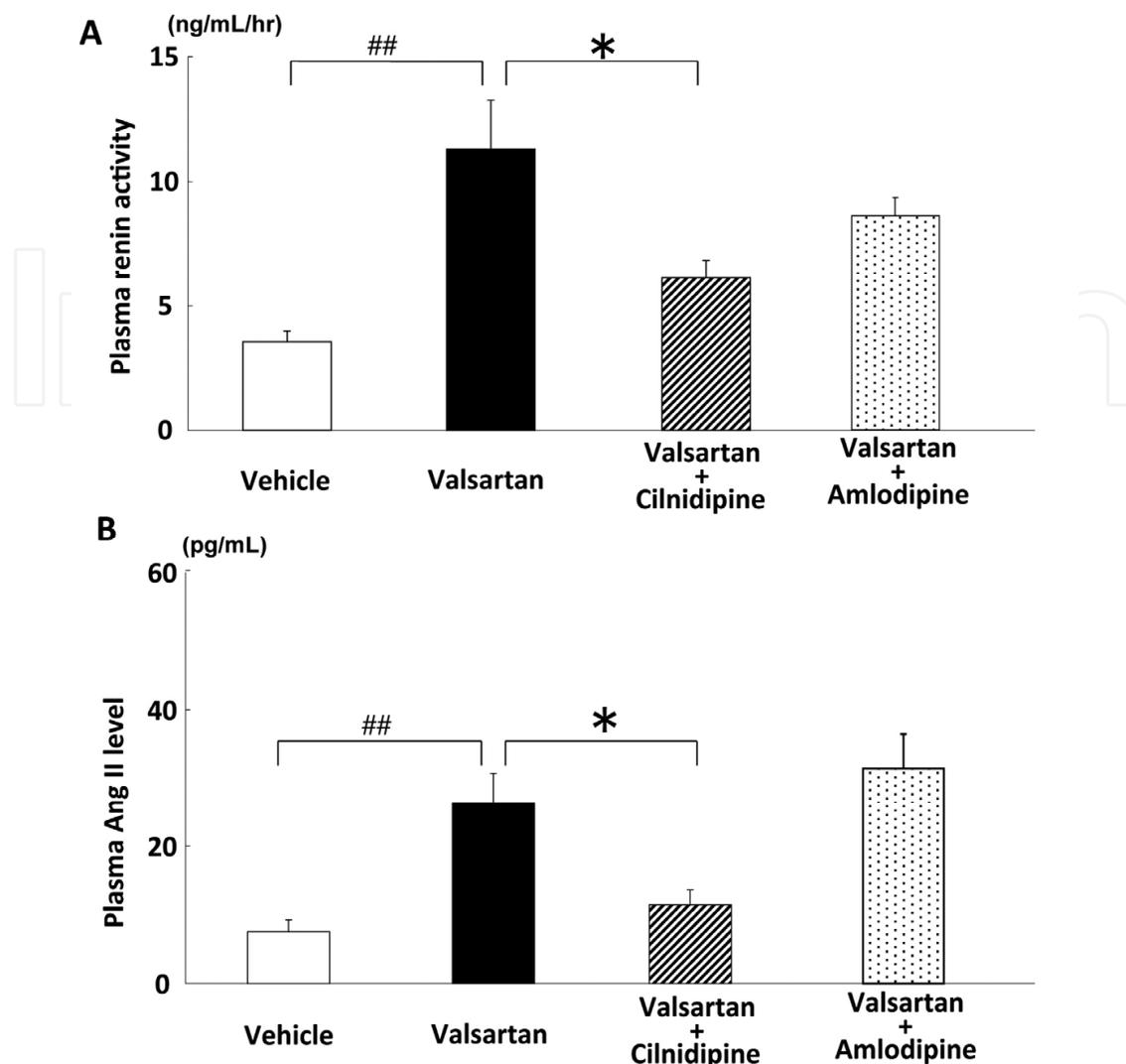


Fig. 3. Effects of combined administration of valsartan and amlodipine or cilnidipine on plasma renin activity (A) and plasma angiotensin II (Ang II) level (B) in spontaneously hypertensive rats. The oral doses of valsartan, amlodipine and cilnidipine were 10, 1 and 1 mg/kg, respectively. Values are expressed as means $\pm$ SE. ##P < 0.01, vehicle vs. valsartan alone, \*P < 0.05, Ca<sup>2+</sup> channel blockers plus valsartan vs. valsartan alone. Data are quoted and modified from Aritomi et al., 2011b.

and aldosterone decreased in the cilnidipine group. On the other hand, elevation of plasma concentrations of angiotensin II and aldosterone was detected in the amlodipine group. Cilnidipine is expected to restore similar electrical remodeling process to pathophysiology of chronic atrioventricular block. Indeed, a recent electrophysiological study has demonstrated that some cardiac K<sup>+</sup> channels ( $I_{Ks}$  and  $I_{to}$ ) are downregulated in the diabetic canine heart, leading to QT interval prolongation. Long QT interval has also been reported in patients with various cardiovascular diseases including hypertension with hypertrophy, hypertrophic cardiomyopathy and end-stage renal failure (Takahara et al., 2009). Therefore, long-term blockade of L/N-type Ca<sup>2+</sup> channels may ameliorate the ventricular electrical remodeling in the hypertrophied heart leading to QT-interval prolongation, which will provide a novel therapeutic strategy.

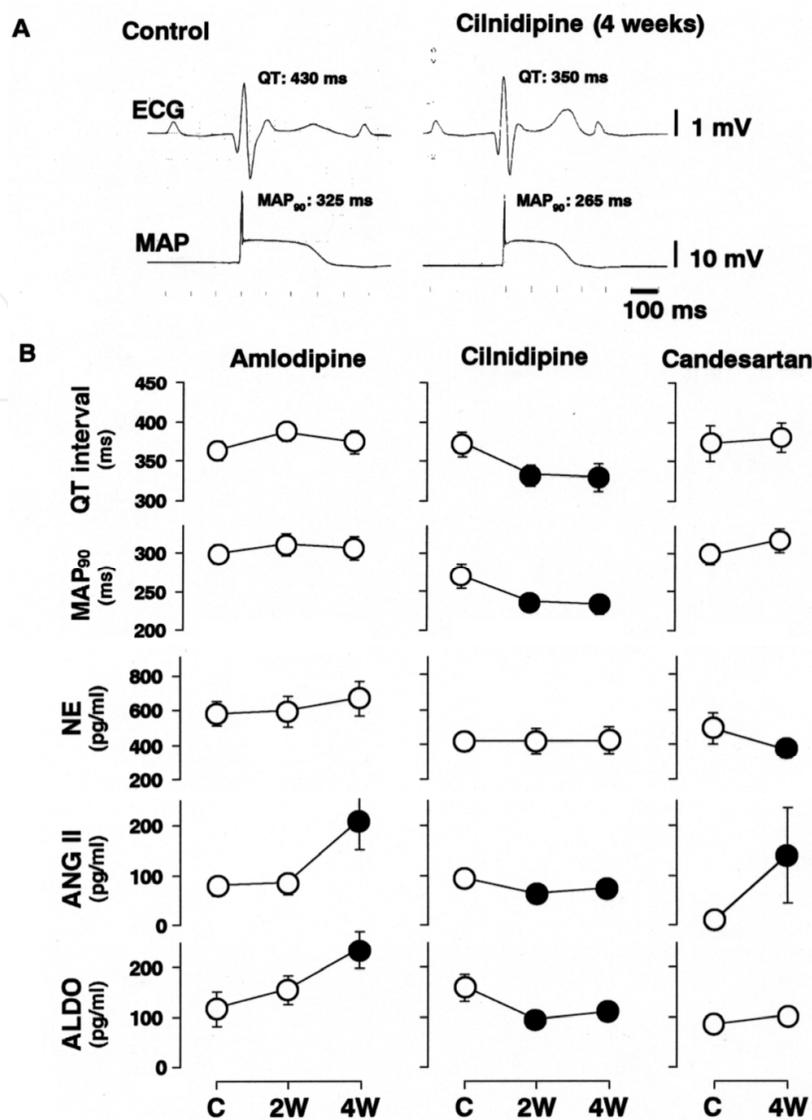


Fig. 4. Effects on electrocardiogram (ECG) and monophasic action potential (MAP) signal during idioventricular rhythm in chronic atrioventricular block dogs. A: Typical tracings of effects of cilnidipine on ECG and MAP signal. B: Effects of amlodipine (2.5mg/day), cilnidipine (5mg/day) and candesartan (12mg/day) on QT interval, MAP duration and plasma levels of norepinephrine (NE), angiotensin II (ANG II) and aldosterone (ALDO). These parameters were obtained at pre-drug control (C) and 2 weeks (2W) and 4 weeks (4W) after the start of drug daily administration. Data are presented as the means $\pm$ SE. Closed symbols represent the significant differences from each pre-drug control (C) value by  $p < 0.05$ . Data are quoted and modified from Takahara et al., 2009.

## 5. Conclusion

Cilnidipine is a promising  $\text{Ca}^{2+}$  channel blocker as the 4th generation with a rational pharmacological profile; i.e. dual L/N-type  $\text{Ca}^{2+}$  channel-blocking action. The blockade of N-type  $\text{Ca}^{2+}$  channels effectively suppresses neurohumoral regulation in the cardiovascular system, including sympathetic nervous system and renin-angiotensin-aldosterone system. Thus, cilnidipine is expected to be favorable for various types of complication of

hypertension. Indeed, its advantage is demonstrated by the clinical study showing that cilnidipine is superior to amlodipine in preventing the progression of proteinuria in patients with hypertension and chronic renal disease (Fujita et al., 2007). The currently described information suggests that cilnidipine is a new type of antihypertensive drug distinguished from other L-type Ca<sup>2+</sup> channel blockers or even other antihypertensives, which will be useful for selection of antihypertensive drugs according to the pathophysiological condition of a patient.

## 6. References

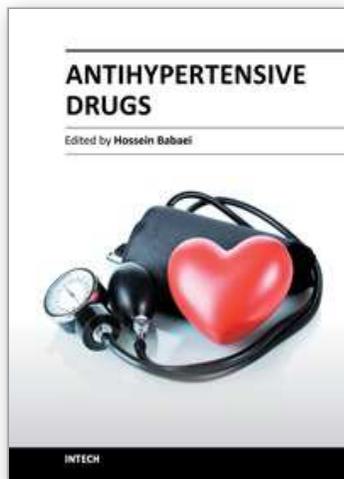
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Hypertension, known as a "silent killer" is widely prevalent and a major risk factor for cardiovascular diseases. It afflicts more than one billion population worldwide and is a leading cause of morbidity and mortality. The authors of the chapters look from different angles to hypertension, sharing their new knowledge and experience in the direction of deep understanding and more clarification of the disease providing an invaluable resource not only for clinicians, but also for all medical sciences students and health providers.

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