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Ruschitzka FT, Lüscher TF, Noll G

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Calcium antagonists and endothelial function

F. T. Ruschitzka, G. Noll, T. F. Lüscher

Endothelial cells release numerous vasoactive substances, such as nitric oxide and endothelin-1. As endothelial dysfunction has been recognized as an early event in cardiovascular disease, modern therapeutic strategies in coronary artery disease should focus on preserving or restoring endothelial integrity.

Calcium antagonists are widely used in the treatment of cardiovascular diseases. Three main chemical classes of calcium antagonists have been delineated: (1) phenylalkylamines (ie, verapamil, gallopamil), (2) dihydropyridines (ie, nifedipine as well as second generation dihydropyridines) and (3) benzothiazepines (ie, diltiazem). All drugs bind to different sites at the L-type calcium channel and thereby reduce the influx of extracellular calcium into the cell. Mibefradil also blocks T-type calcium channels and represents a new class of calcium channel blockers, but has been withdrawn from the market due to druginteraction

The formation of NO from L-arginine by the enzyme NO synthase is associated with an increase in intracellular Ca^{2+}. Although an increase in intracellular Ca^{2+} is probably most important for the release of NO, acute treatment with Ca^{2+} antagonists may directly stimulate NO release as well as facilitate the effects of NO at the level of vascular smooth muscle cells. Chronic treatment with Ca^{2+} antagonists was shown to prevent or restore decreased endothelium-dependent relaxations via increased NO production, augmented sensitivity of the vascular smooth muscle to endothelium-derived NO or potentiation of NO independent vasodilatory systems.

Endothelins exert their biological effects via activation of specific membrane bound receptors that are coupled to G-proteins. Two types of endothelin receptors have been cloned, ie, ET_A- and ET_B- receptors. Calcium antagonists counteract the effects of ET-1 at the level of vascular smooth muscle by reducing Ca^{2+}-inflow and facilitating the vasodilator effects of NO. As small vessels appear to be more dependent on extracellular Ca^{2+} than larger vessels, Ca^{2+} antagonists are preferentially effective in attenuating endothelin-induced vasoconstriction in the resistance circulation in vitro and in vivo.

Ongoing clinical trials have to clarify whether these beneficial effects of Ca^{2+} antagonists on early endothelial dysfunction are associated with improvement of prognosis for our patients with cardiovascular disease. *J Clin Basic Cardiol 1999; 2: 175–80.*

Key words: calcium antagonists, endothelium, nitric oxide, endothelin-1

Coronary artery disease and its sequelae remain the most important cause of morbidity and mortality in Western countries. Although substantial advances have been made in the past two decades in the surgical, interventional, and medical therapy of these conditions, it became clear that only a better understanding of the cellular and molecular mechanisms could be the basis for rational mechanistic approaches and, in turn, for cause-oriented therapy of cardiovascular diseases. Because of their strategic anatomic position between the circulating blood and vascular smooth muscle, the center of interest has recently focused on endothelial cells [1]. Indeed, although they were originally considered the "wallpaper" of the blood vessel, with no major functional properties, it has now been recognized that the endothelial cells are a rich source of vasoactive substances [2]. Endothelial cells produce not only relaxing factors such as nitric oxide (NO) and prostacyclin but also contracting factors such as endothelin (ET), cyclooxygenase products (thromboxane A_2, prostaglandin H_2, and superoxide anions), and are also involved in fht formation of angiotensin II [1, 3–5].

The effects of cardiovascular drugs on endothelium and vascular smooth muscle function are important for the prevention of cardiovascular disease. Changes in endothelial function are an early event in most forms of cardiovascular diseases and, later in the disease process, vascular smooth muscle cells are functionally altered and begin to migrate to, and proliferate in the intima [1]. Calcium (Ca^{2+}) antagonists are widely used in patients with cardiovascular disease and are thought to have vascular protective effects, although their safety has been under discussion recently [6].

Calcium antagonists

The regulation of intracellular Ca^{2+} plays a crucial role as a determinant of vascular tone of all blood vessels [7]. Contractile responses are initiated and maintained by an increase in intracellular Ca^{2+}; this increase can be derived from intracellular stores and/or from extracellular sources through Ca^{2+} channels (Fig. 1) [7]. Ca^{2+} antagonists inhibit transmembrane Ca^{2+} influx via voltage-operated Ca^{2+} channels into vascular smooth muscle and (depending on the molecule) also in myocardial cells [7, 8]; the latter effect explains their negative inotropic properties, whereas the former is responsible for their potent vasodilator effects.

Despite markedly different chemical structures, all compounds of the three main classes of Ca^{2+} antagonists (dihydropyridines, phenylalkylamines, and benzothiazepines) inhibit the inward flow of Ca^{2+} ions through the slow (L-type) Ca^{2+} channels (Fig. 1) [9]. However, because of binding at different receptor sites, different pharmacokinetic properties, and different effects at the levels of the cardiovascular (coronary and peripheral arteries, cardiac conduction system, and myocardium) and extracardiovascular systems, each of these compounds has its own advantages and disadvantages [9]. Mibefradil (Ro 40-5967) is a novel Ca^{2+} antagonist from the new chemical structural class of benzimidazolyl-substituted tetraline derivatives [10]. Mibefradil blocks L- and T-type Ca^{2+} channels, with a more selective blockade of T-type channels, whereas other Ca^{2+} antagonists block only the L-type channels (Fig. 1) [11]. Mibefradil is a potent direct vasodilator, elicits endothelium-dependent relaxations and facilitates the effects of nitric oxide on vascular smooth muscle [10]. However, mibefradil has been withdrawn from the market due to interactions with other drugs [12–14].

From the Cardiology Division, University Hospital Zürich, Switzerland
Correspondence to: Thomas F. Lüscher, MD, FRCP, Professor and Head of Cardiology, University Hospital, CH-8091 Zürich/Switzerland
e-mail: frankr@physiol.unizh.ch.

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Figure 1. Calcium channels in vascular smooth muscle cells: Contractile responses of vascular smooth muscle cells are initiated and maintained by an increase in intracellular Ca^{2+}; this increase can be derived from intracellular stores and/or from extracellular sources through Ca^{2+} channels. Ca^{2+} antagonists inhibit transmembrane Ca^{2+} influx via voltage-operated Ca^{2+} channels into vascular smooth muscle. All compounds of the three main classes of Ca^{2+} antagonists (dihydropyridines, phenylalkylamines, and benzothiazepines) inhibit the inward current of Ca^{2+} ions through the slow (L-type) Ca^{2+} channels. Mibefradil (Ro 40-5967) is a novel Ca^{2+} antagonist which blocks L- and T-type Ca^{2+} channels, with a more selective blockade of T-type channels, whereas other Ca^{2+} antagonists block only the L-type channels. CRAC = calcium release-activated calcium channel. CA kinase=cyclic AMP-dependent protein kinase. IP_3 = Inositol triphosphate.

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Figure 2. The L-arginine/NO pathway in the blood vessel wall: Endothelial cells form nitric oxide (NO) from L-arginine via the activity of a constitutive nitric oxide synthase (eNOS), which can be inhibited by analogues of the aminoacid such as NO-monomethyl-L-arginine (L-NMMA) or NO-nitro-L-arginine methylester (L-NAME). NO activates soluble guanyl cyclase (sGc) in vascular smooth muscle and platelets, and it causes increases in cyclic 3'5'-guanosine monophosphate (cGMP), which mediates relaxation and platelet inhibition, respectively. In addition, vascular smooth muscle cells can form NO via the activity of an inducible form (by bacterial lipopolysaccharide, tumor necrosis factor-α, interferon-γ and interleukin-1 β) of NO synthase (iNOS). GTP = Guanosin triphosphate.

The vasodilator effect of Ca^{2+} channel blockers can be explained by their inhibitory effect on vascular smooth muscle function [15]. In addition, these agents may cause dilation by interfering with endothelium-dependent responses [15]. Indeed, endothelial cells modulate the degree of contraction of the underlying vascular smooth muscle by the release of relaxing (endothelium-derived relaxation (EDRF) and hyperpolarizing (EDHF) factors), and contracting (endothelium-derived contracting (EDCF)) factors [1, 3, 16]. Release of both types of substances require an increase in endothelial cytosolic Ca^{2+} concentration.

Calcium antagonists and NO

Introduction

Endothelium-derived relaxation factor (EDRF) was discovered more than a decade ago and recently has been confirmed to be identical to nitric oxide (NO, Fig. 2) [3, 17]. NO has been determined to be a unique, ubiquitous messenger of cellular signals. NO is not only involved in the regulation of blood pressure but also has been characterized as a neurotransmitter and plays an important role in the immune system [18].

NO is made by NO synthase in a reaction that converts arginine and oxygen into citrulline and NO. The mechanism of NO synthesis is not completely understood, but it involves the transfer of electrons between various cofactors, including flavin adenin dinucleotide, flavin mononucleotide, nicotinamide adenine dinucleotide phosphate, tetrahydrobiopterin, and heme. Finally, one atom of oxygen binds with the terminal guanidine nitrogen from arginine to form NO [19].

Although several NO synthase isoforms have been isolated, all are homologous and divided into two categories with different regulation and activities. The constitutive isoforms in neuronal and endothelial cells are always present [20, 21]. These NO synthase isoforms are inactive until intracellular Ca^{2+} levels increase, the Ca^{2+} binding protein calmodulin binds to Ca^{2+}, and the Ca^{2+}-calmodulin complex binds to and activates NO synthase [22, 23]. The constitutive NO synthase isoforms then synthesize small amounts of NO until intracellular Ca^{2+} levels decrease. In contrast, the inducible NO synthase isoform is normally not expressed in macrophages and hepatocytes. When activated by specific cytokines, these cells produce an inducible NO synthase enzyme that synthesizes large amounts of NO [24].

Physiology

Although most available Ca^{2+} channel blockers usually do not affect endothelium-dependent relaxations, diltiazem and its analogue TA 3090 at high concentration inhibit release of EDRF [25], whereas dihydropyridines such as nitrendipine, nifedipine, nisoldipine and nimodipine augment its release [26]. Furthermore, the new Ca^{2+} antagonist mibefradil causes release of EDRF in canine arteries as was already suggested by the observation that mibefradil causes more pronounced and more rapid relaxations in rings of canine femoral arteries with than without endothelium. This conclusion is strengthened by the experiments in carotid arteries with endothelium studied under bioassay conditions, which demonstrated that release of a diffusible endothelial factor, which relaxes vascular smooth muscle, is involved in the early response to mibefradil [27].

Epicardial but not intramyocardial porcine coronary arteries preincubated in vitro with the Ca^{2+} antagonist mibefradil exhibit augmented endothelium-dependent relaxations to bradykinin (Fig. 3) [28]. That the endothelium-independent relaxation to sodium nitroprusside, which as an exogenous NO donor, causes relaxations through the formation of cyclic GMP, is also augmented in epicardial arteries, strongly indicates that mibefradil facilitates the effects of NO at the level of vascular smooth muscle in these arteries also [28]. In the presence of mibefradil, the intracellular Ca^{2+} concentration in vascular smooth muscle may be lower, allowing cyclic GMP to mediate relaxations more effectively.

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Figure 3. Effects of mibefradil on endothelium-dependent (left panel) and -independent relaxation (right panel) of epicardial coro-nary arteries precontracted maximally by U 46619. In the presence of mibefradil, concentration-response curves to bradykinin and sodium nitroprusside were shifted to the left (P < .05 vs. control).

Although the inducible NO synthase is Ca^{2+} independent, the dihydropyridine Ca^{2+} channel antagonists, nifedipine, manidipine, nitrendipine, benidipine, barnidipine, perdipine, and nilvadipine all reduce bacterial lipopolysaccharide induced NO production in cultured macrophages [29].

Thus, in certain preparations, acute treatment with Ca^{2+} antagonists may directly stimulate NO release as well as facilitate the effects of NO at the level of vascular smooth muscle cells. However, no data are available for human blood vessels so far.

In normotensive Wistar-Kyoto (WKY) rats, chronic treatment for 8 weeks with nifedipine (10 mg/kg/day) does not affect blood pressure or endothelium-dependent relaxations to acetylcholine in isolated coronary arteries [30]. Since in these blood vessels endothelium-derived NO fully accounts for relaxations induced by acetylcholine this suggests that chronic nifedipine therapy does not improve endothelial NO release in these normotensive animals [30]. Similar results were obtained in normotensive salt resistant Dahl rats. Chronic treatment of these animals with mibefradil also does not alter endothelium-dependent relaxations to acetylcholine, adenosine-diphosphate and thrombin in isolated aortic ring-preparations [27].

In WKY as well as salt resistant Dahl rats chronic treatment with nifedipine or mibefradil did not affect endothelium-independent relaxations to nitrovasodilators, suggesting that chronic administration of Ca^{2+} antagonists does not augment sensitivity of vascular smooth muscle to endothelium-derived NO [27, 30].

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Figure 4. Graph showing the effect of chronic antihypertensive therapy in spontaneously hypertensive rats (SHR) with the Ca^{2+} antagonist nifedipine (10 mg/kg^{-1}/day for 8 weeks) on endothelium-dependent relaxations to acetylcholine (left) and endothelium-independent relaxations to the nitric oxide donor 3-morpholino-sydnonimine (SIN-1; right). Note that both the sensitivity and potence of the endothelium-dependent vasodilator acetylcholine were increased in the nifedipine group (P < .05), whereas the responsiveness of vascular smooth muscle to SIN-1 remained unaffected.

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Figure 5. Concentration-response curves to acetylcholine in mesenteric resistance arteries. Long-term (a) and short-term (b) treatments with placebo (control), L-NAME, L-NAME plus verapamil, and L-NAME plus trandolapril (or trandolaprilat). Results are shown as mean ± SEM (n = 6 to 8) and expressed as percentage of the increase in the intraluminal vascular diameter from the pre-contracted condition by norepinephrine (2 x 10^{-6} mol/L). *P < .05 vs. control group, †P < .05 vs. L-NAME group.

Hypertension

In mesenteric resistance arteries and renal arteries obtained from L-NAME hypertensive WKY rats, relaxations to acetylcholine are not improved by short-term (30 minutes) in vitro preincubation with the Ca^{2+} antagonist verapamil [31].

Impaired endothelium-dependent relaxations occur in experimental [32–34] models as well as in human essential hypertension [35, 36]. Several studies on various models of experimental hypertension have shown beneficial effects of Ca^{2+} antagonists either to prevent or to restore endothelial function. The mechanism of this beneficial effect, however, is different in different models of hypertension.

In coronary arteries obtained from spontaneously hypertensive rats, chronic antihypertensive therapy with the Ca^{2+} antagonist nifedipine improves endothelium-dependent relaxations to acetylcholine, whereas the responsiveness of vascular smooth muscle to NO remains unchanged (Fig. 4) [30]. Since NO fully accounts for endothelium-dependent relaxations to acetylcholine, this indicates that NO production is improved by chronic therapy with Ca^{2+} antagonists in rat coronary arteries [30].

The chronic treatment with mibefradil potentiates endothelium-dependent relaxations to acetylcholine, adenosine-diphosphate and thrombin in aortic ring-preparations from salt-sensitive Dahl rats [27]. In these animals, the treatment also augments the relaxations of aortic ring-segments without endothelium to the NO donor linsidomine (SIN-1) [27]. Thus, the potentiation of endothelium-dependent relaxations can be explained in part by an augmented sensitivity of the vascular smooth muscle to endothelium-derived NO.

Chronic treatment with verapamil prevents the increase in systolic blood pressure and the blunted acetylcholine-induced relaxations of mesenteric resistance arteries and renal arteries that occurred with L-NAME treatment of WKY rats (NO-deficient hypertension) (Fig. 5) [31]. Since NO synthase activity remains unaltered, this indicates that the endothelial function can be preserved with Ca^{2+} antagonists by a mechanism independent of NO production [31]. Hence, in long-term NO deprivation, verapamil can potentiate other alternative vasodilatory systems that normally do not play a significant role in maintaining vascular tone.

Calcium antagonists and endothelin

Endothelins

After it had been noted that cultured endothelial cells of various species including humans produce not only relaxing factors, but also a potent vasoconstrictor substance [37], Yanagisawa et al. demonstrated that this vasoconstrictor activity of the endothelium is related to the formation of a 21-amino acid peptide, endothelin (ET) [4, 38]. Three forms of the peptide have been characterized: endothelin-1 (ET-1), endothelin-2 (ET-2) and endothelin-3 (ET-3) [38, 39]. Endothelial cells appear to produce ET-1 exclusively. ET is generated from precursor molecules (ie, preproendothelin, a 203-amino acid peptide and proendothelin or big endothelin, a peptide containing 92 amino acids [4]. Big endothelin-1 is converted to the 21-residue peptide by the endothelin-converting enzymes (ECE), an essential step for the expression of the full vasoconstrictor activity [38].

ET-1 is a potent vasoconstrictor both *in vitro* and *in vivo* [40–42]. Its effects are long-lasting and – particularly in isolated blood vessels – difficult to wash out, presumably because the peptide binds tightly to its receptor. In the internal mammary and coronary artery, low and threshold concentrations of ET-1 (which exert no significant contractile effect) potentiate the response to other vasoconstrictor hormones such as exogenous norepinephrine or that released from adrenergic nerve endings or serotonin [43, 44]. In addition, ET can activate endothelial cells to release relaxing factors, such as prostacyclin and NO. Furthermore, it has been shown that NO inhibits ET synthesis in the intact porcine aorta [45].

Calcium antagonists and endothelin release

The production of endothelin-1 in endothelial cells (eg porcine aorta) is associated with an increase in intracellular Ca^{2+} [45]. Thus, Ca^{2+} ionophore A23187, which increases intracellular Ca^{2+} levels in endothelial cells, is a very potent stimulator of endothelin-1 production [45].

Interestingly, in most experimental studies, prevention of Ca^{2+} influx does not inhibit endothelin release.

Pulmonary hypertension

Goerre et al. have shown that the degree of hypoxia-induced acute pulmonary hypertension correlates with increased plasma ET-1 levels in healthy mountaineers [46]. The Ca^{2+} antagonist nifedipine, however, did not affect plasma ET-levels [46].

This may be due to the fact that Ca^{2+} increase in endothelial cells is derived primarily from intracellular sources (via activation of phospholipase C and inositol triphosphate) [47] and not through voltage-operated Ca^{2+} channels, which are not expressed in the endothelial cell membrane.

Cardiovascular surgery

Patients undergoing coronary artery bypass grafting show elevated endothelin plasma levels during and after surgery [48]. Interestingly, ET-levels are lower in patients receiving diltiazem than those receiving nitroglycerin (both $p < 0.01$) [48].

These data demonstrate that diltiazem is more effective than nitroglycerin in preventing ET increase during cardiovascular surgery.

Calcium antagonists and response to endothelin

Although ET was originally considered to be an endogenous activator of voltage-operated Ca^{2+} channels [4], it has now been shown that ET interacts with specific receptors on vascular smooth muscle (ET_A- and ET_B-receptors), mediating vasoconstriction and proliferation. On endothelial cells, ET interacts with ET_B-receptors, stimulating the formation of NO and PGI_2 [49, 50].

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Figure 6. Effects of endothelin-1 in the human forearm circulation in the presence and absence of Ca^{2+} antagonists. Both nifedipine as well as verapamil prevent the decrease in forearm vascular resistance occurring with higher concentrations of endothelin (25 and 50 ng/ml/100 ml forearm vascular tissue) and unmask the vasodilator effects, which is also operative at this level of endothelin concentrations.

Macrovessels

In certain blood vessels, such as the porcine coronary artery, endothelin receptors on vascular smooth muscle are linked to voltage-operated Ca^{2+} channels via G_i-proteins [51]. This may explain why Ca^{2+} antagonists reduce endothelin-induced vasoconstriction in these vessels and are similarly effective in the human coronary artery [52]. In other blood vessels, eg, the human internal mammary artery [8], most of the contractile effects induced by ET are mediated by release of Ca^{2+} from intracellular stores (after activation of phospholipase C with formation of inositol triphosphate and diacylglycerol) [47, 53], and therefore Ca^{2+} antagonists are unable to prevent ET-induced contractions.

Interestingly, Ca^{2+} antagonists can reverse endothelin-induced contractions in both the porcine coronary artery [28] as well as the human internal mammary artery [8]. The probable reason for this is that, in contracting cells, ET lowers the membrane potential of vascular smooth muscle cells [54], opening voltage-operated Ca^{2+} channels. Therefore, once contractions have developed, Ca^{2+} antagonists are able to exert an inhibitory effect.

Microvessels

Several studies have suggested that small vessels are more dependent on the influx of extracellular Ca^{2+} than larger vessels [55]. Indeed, intramyocardial and epicardial coronary arteries exhibit a differential sensitivity to Ca^{2+} channel blockade by the novel Ca^{2+} antagonist mibefradil [28]. Although mibefradil is effective both in reversing and preventing contractions to ET-1 in isolated blood vessels, the effects of the Ca^{2+} antagonist are much more pronounced in intramyocardial than epicardial vessels, particularly when mibefradil is added after a contraction has been established [28]. Furthermore it has been shown that dihydropyridines such as lacipine and nifedipine strongly reduce contractions to endothelin-1 in porcine ciliary arteries with a diameter of 250 μm and less [56]. This may also explain why, in the human forearm microcirculation of normal subjects, intraarterial administration

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Figure 7. Effects of orally administered slow-release diltiazem (240 mg) on vasoconstriction to exogenous endothelin (10–12 mol intradermally) at the injection site in the human skin microcirculation *in vivo* in patients with coronary artery disease. Data are shown as differences from saline from the area under the time-response curve (0 to 10 minutes after injection). Asterisks indicate statistical significance vs. saline (***P < . 001). PU indicates perfusion units.

of verapamil or nifedipine fully prevents ET-induced contractions (Fig. 6) [41]. Interestingly, in patients with coronary artery disease orally administered slow-release diltiazem inhibits vasoconstriction to exogenous endothelin in the human skin microcirculation (Fig. 7) [57]. Further studies are required to clarify the potential usefulness of Ca^{2+} antagonists in clinical disease states associated with increased endothelin production.

Potentiating effect of endothelin

Interestingly, subthreshold concentrations of ET potentiate contractions to serotonin and norepinephrine [43, 44, 58]. Indeed, ET markedly augments the contractile responses to serotonin and norepinephrine in the human mammary and coronary artery [43]. These indirect effects appear to be attributable to the increased sensitivity of the vascular smooth muscle to Ca^{2+}, and are prevented by pretreatment with Ca^{2+} antagonists of the dihydropyridine type [43] as well as by the non-dihydropyridine Ca^{2+} antagonist mibefradil [59].

Conclusion

Changes in endothelial function are an early event in most forms of cardiovascular diseases. Ca^{2+} antagonists inhibit transmembrane Ca^{2+} influx via voltage-operated Ca^{2+} channels into vascular smooth muscle cells. Calcium antagonists are mainly involved in preventing the effects of endothelium-derived contracting factors, such as ET-1 at the level of vascular smooth muscle by reducing Ca^{2+} inflow. In addition, Ca^{2+} antagonists may either directly stimulate NO release or facilitate the effects of endothelium-derived NO. Ongoing clinical trials [60] will clarify whether the beneficial effects of Ca^{2+} antagonists on early endothelial dysfunction are associated with the regression of atherosclerosis for the benefit of our patients with cardiovascular diseases.

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