Effects of Calcium and Its Antagonists on the Canine Mesenteric Circulation

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SUMMARY We studied circulatory and metabolic responses of the intestinal circulation to intraarterial infusions of solutions containing calcium chloride or calcium antagonists in anesthetized dogs. Measurements included blood flow to the terminal ileum, arteriovenous oxygen content difference, distribution of radiolabeled microspheres to the mucosal-submucosal compartment and intraluminal pressure. Calculated parameters included oxygen consumption and fractional mucosal-submucosal blood flow. Both calcium antagonists, nifedipine and diltiazem, increased intestinal blood flow, mainly to the mucosa-submucosa, depressed intestinal motility, and did not change oxygen consumption. Thus, both agents appear to act mainly on resistance vessels without increasing the nutrient circulation. Calcium chloride (1.0-500.0 μg/kg per min) had a mild constrictor effect; at a dose of 1000.0 μg/kg per min, calcium chloride became a dilator agent in the mesenteric circulation. The dilator effect of the highest dose of calcium was reversed by digoxin, suggesting the involvement of Na⁺,K⁺-ATPase. Nifedipine completely blocked calcium-induced constriction of the intestinal circulation and partly inhibited norepinephrine-induced constriction. Studies on isolated mesenteric arterial smooth muscle revealed that nifedipine relaxed KCl-contracted strips in the presence of external calcium and relaxed norepinephrine-contracted strips in both the presence and absence of external calcium. These in vitro findings suggest that calcium antagonists interfere with the release of calcium from intracellular sites as well as with the slow inward current of calcium. Circ Res 48: 692-700, 1981

CALCIUM IONS (Ca²⁺) play a central role in the control of smooth muscle contractility. Various stimuli initiate contraction of vascular smooth muscle by increasing the concentration of free Ca²⁺ in the cytoplasm, thereby activating contractile proteins (Somlyo and Somlyo, 1970; Johansson, 1978; Winquist and Bevan, 1980). There are two main sources of activator Ca²⁺, namely, the pool of extracellular Ca²⁺ including ions loosely bound to the external muscle membrane and the tightly bound Ca²⁺ which is sequestered inside the muscle fiber, especially within the cell membrane, sarcoplasmic reticulum, and mitochondria (Hurwitz and Suria, 1971; Bohr, 1978; Johansson, 1978; van Breeman et al., 1979). Different contractile agonists have been


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shown to influence the two sources of Ca\textsuperscript{2+} differently. For instance, contraction induced by depolarizing concentrations of potassium is the result of an augmented flux of Ca\textsuperscript{2+} from the extracellular space, whereas the vasoconstriction induced by noradrenaline involves primarily the release of intracellular Ca\textsuperscript{2+} (Hudgins and Weiss, 1968; Seidel and Bohr, 1971; Godfraind and Kaba, 1972; Bohr, 1978).

Effects of Ca\textsuperscript{2+} on the intestinal circulation have not been studied extensively and vascular responses appear minimal (Chou et al., 1963; Dabney et al., 1979). These compounds are potent coronary vasodilators, relaxing primarily the smooth muscle of large arteries, and, therefore, are potentially useful agents for the management of intestinal ischemia would appear justified.

Effects of calcium antagonists in the intestinal circulation have received little attention (Schwaiger et al., 1977). Since such pathological changes also occur in the mesenteric vasculature (Marston, 1977; Bynum and Jacobson, 1979) a search among the calcium antagonists for a potentially useful agent for the management of intestinal ischemia would appear justified.

The aim of our present study was to investigate the effects of calcium and two calcium antagonists, nifedipine and diltiazem, on the intestinal circulation, its oxygen consumption, and the distribution of intestinal blood flow in vivo. Attempts also were made to elucidate the mechanism of action of nifedipine on mesenteric arterial smooth muscle in vitro.

**Methods**

A total of 29 mongrel dogs of both sexes, weighing between 16 and 28 kg (average 20.6 kg) were used in this study. Of these animals, 25 were studied during a control period and during administration of drugs. After each experiment, control and experimental intestinal segment were removed, rinsed, and weighed. Segments were opened along the mesenteric border and cut into portions about 10 cm long. The mucosal and submucosal layers were stripped from the muscularis and counted in a γ spectrometer (Packard Instruments). Corrections were made for overlap in the energy spectra. Fractional blood flow to the mucosal-submucosal compartment (FF\textsubscript{m-s}) was calculated as the product of BF and the percentage of microspheres distributed to the mucosa-submucosa (m-s) and was expressed in ml/min per 100 g of intestine.

Changes in blood flow distribution within the intestinal wall were assessed with four radiolabeled microspheres (\textsuperscript{51}Cr, \textsuperscript{51}Sr, and \textsuperscript{85}Sr) of 15 ± 3 μm diameter (3M Co.) injected into the left ventricle during a control period and during administration of drugs. After each experiment, control and experimental intestinal segment were removed, rinsed, and weighed. Segments were opened along the mesenteric border and cut into portions about 10 cm long. The mucosal and submucosal layers were stripped from the muscularis and counted in a γ spectrometer (Packard Instruments). Corrections were made for overlap in the energy spectra. Fractional blood flow to the mucosal-submucosal compartment (FF\textsubscript{m-s}) was calculated as the product of BF and the percentage of microspheres distributed to the mucosa-submucosa (m-s) and was expressed in ml/min per 100 g of intestine.

Following surgery and a 30-minute stabilization period, dose-response curves for ia infusions of nifedipine (Pfizer Pharmaceuticals), diltiazem (Mar-
Laplace). Contractile activity was determined as isometric tension on a Grass model 7 polygraph.

Strips were stretched passively to optimal length and the polyethylene tubing conveying the drug to the mesenteric artery were wrapped in aluminum foil. The pump, syringe, tubing, and dog weighed the drug in a dark room on a balance until the response obtained was reproducible. Then strips were contracted by adding either KCl to give a concentration of 30 mM or 0.1 μM norepinephrine (Levophed bitartrate, Winthrop Laboratories) in order to compare the potency of agonists, and to assess possible changes in tension related to time. Reproducibility of contractile responses to both agonists in each type of PSS was also evaluated in separate experiments in which strips were repetitively contracted at 20-minute intervals. Cumulative dose-response curves (10⁻⁹ to 10⁻⁵ M) for nifedipine were determined in strips contracted with 30 mM KCl or 0.1 μM norepinephrine in normal PSS, in strips contracted with 0.1 μM norepinephrine in Ca²⁺-free PSS and Ca²⁺-free PSS with EGTA, and in strips 20 minutes after obtaining dose-response relationships for nifedipine and washing the chambers several times with appropriate PSS. The response of strips to KCl and norepinephrine were assessed again a few times during the subsequent 2 to 3 hours following drug washout.

Measurements used for statistical analyses under in vivo conditions were obtained at the time of injections of microspheres to correlate changes in distribution of blood flow with those of total blood flow or oxygen consumption. Results have been expressed as the mean percentage of control values ± standard errors of the means (SEM). Changes from control values under both in vivo and in vitro conditions were analyzed with a paired t-test and the differences between series of experiments were analyzed with a pooled t-test. Differences were considered significant at a probability of less than 0.05. Only those changes which were significant are cited in the Results section.

### Results

#### In Vitro Studies

Control values for 25 dogs were: BF 65.6 ± 4.7 ml/min per 100 g of intestinal tissue, A-VO₂ 3.1 ± 0.3 ml O₂/ml of blood, VO₂ 2.0 ± 0.2 ml O₂/min per 100 g of intestine, the fraction of total blood flow which perfused the muscularis 30.6 ± 3.5%, m-s 69.4 ± 3.5%, FBFm-s 45.0 ± 3.4 ml/min per 100 g of intestine, and IP 4.8 ± 0.7 mm Hg. Systemic arterial pressure was not changed significantly during any series of tests. The weight of intestinal segments averaged 208.5 g.

Infusion of the three doses of nifedipine produced a dose-dependent increase in BF and decreases in A-VO₂ and IP. The two higher doses of nifedipine also caused increases in m-s and FBF m-s. The calculated dose of the drug producing a 50% increase in BF was 0.36 μg/kg per min or 1 × 10⁻⁹ mol/kg per min (Fig. 1).

Diltiazem evoked similar responses, but was less potent. The calculated dose of diltiazem causing a 50% increase in BF was 3.3 μg/kg per min or 7.3 × 10⁻⁹ mol/kg per min (Fig. 2). After cessation of...
infusion of either agent, all measured parameters returned to control within a few minutes.

CaCl₂ produced a dose-dependent decrease in BF up to a dose of 500.0 μg/kg per min. At a dose of 1,000.0 μg/kg per min, CaCl₂ caused a significant increase in BF. A-Vo₂ was increased at all doses of CaCl₂, although at lowest and highest doses the changes were not significant. Vo₂ changed significantly only at the 1,000.0 μg/kg per min dose, when it increased (Fig. 3). IP increased in a dose-dependent manner with the 100.0, 500.0, and 1,000.0 μg/kg per min doses of CaCl₂. The intestinal contractions were of both rhythmic and tonic type and were observed mainly at the beginning of infusion of each dose. Since the distribution of microspheres was not changed significantly at any dose, changes in FBFₘₘₛ paralleled those of BF. These data were omitted for the sake of clarity.

The lowest dose of nifedipine, infused together with the highest constrictor dose of CaCl₂, completely blocked the effects of CaCl₂. Thus, the effects of nifedipine + CaCl₂ were not significantly different from those of nifedipine alone (Fig. 4). Nifedipine also partially inhibited the vasoconstrictor response to norepinephrine. Control infusion of the catecholamine decreased BF, Vo₂, m-s and FBFₘₘₛ and increased A-Vo₂. Norepinephrine infused with nifedipine produced significantly smaller changes in all parameters except Vo₂ than did norepinephrine alone (Fig. 5).

Digoxin reduced BF and Vo₂ and increased A-Vo₂ (Fig. 6). CaCl₂ (1,000.0 μg/kg per min) infused 10-15 minutes after injection of digoxin exerted a small vasoconstrictor effect; thus, BF decreased and A-Vo₂ increased, whereas Vo₂ decreased when compared with control values before digoxin. BF and A-Vo₂ were significantly different from values observed with digoxin alone.

In Vitro Experiments

KCl (30 mM) and norepinephrine (0.1 μM) were equipotent in contracting strips of mesenteric artery in normal PSS, i.e., contractile tensions obtained with both agonists were not significantly different. As shown in Figure 7 in normal PSS, mean control
tension obtained with KCl was 8.2 ± 0.8 g and that obtained with norepinephrine was 9.6 ± 1.1 g in the same strips. In calcium-free PSS, control tension obtained with KCl was reduced to 1.5 ± 0.2 g and in the same strips norepinephrine induced a tension of 7.4 ± 1.2 g. These values were significantly different (P < 0.001). In calcium-free PSS with EGTA, KCl-contracted strips developed a tension of 0.7 ± 0.1 g, whereas norepinephrine-induced contractions of the same series of strips averaged 5.0 ± 1.1 g. These values again were significantly different (P is less than 0.005).

Additional control tests involved repetitive challenges with either agonist in normal PSS and Ca²⁺-free PSS with EGTA. Contractile responses to consecutive challenges with KCl were not different from one another and were very well sustained so long as the excess of KCl was not washed out. Responses to consecutive challenges with norepinephrine in normal PSS were also not different from one another and were well sustained; however, in Ca²⁺-free PSS and Ca²⁺-free PSS with EGTA, contractile responses to norepinephrine reached their maxima within 1-2 minutes and then decreased at a steady rate. Therefore, in experiments in which norepinephrine was used as the contractile agonist, before assessing the effects of nifedipine, the rate of spontaneous decrease in tension was established for each strip over a period of 30-35 minutes, and decreases in tension obtained with increasing concentrations of nifedipine then were...
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Figure 6 Comparison of the effects of CaCl₂ (dilator dose) before and after digoxin. ↑ indicates significant difference between digoxin alone and digoxin + CaCl₂. Other symbols as in Figure 1.

Corrected for the spontaneous decrease in tension during the control test for each corresponding period of time.

Nifedipine administered in concentrations increasing from $10^{-9}$ to $10^{-5}$ M every 5 minutes pro-

Figure 7 Responses of mesenteric arterial strips (n = 7) to KCl and norepinephrine (NE) in normal PSS and to norepinephrine in Ca²⁺-free PSS and Ca²⁺-free PSS with EGTA before and after administration of nifedipine. * indicates a significant effect of nifedipine. Two asterisks indicate significant difference from both norepinephrine-induced contraction in normal and Ca²⁺-free PSS. Other symbols as in Figure 1.

FIGURE 8 Dose-responses to nifedipine ($10^{-9}$ to $10^{-5}$ M) obtained in four series of seven strips, namely, KCl-contracted in normal PSS and NE-contracted in normal PSS. Each curve represents means ± SEM from seven different strips from two dogs. Other symbols as in Figure 1.

Nifedipine administered in concentrations increasing from $10^{-9}$ to $10^{-5}$ M every 5 minutes produced a concentration-dependent relaxation of KCl-contracted strips in normal PSS and of strips contracted with norepinephrine in normal PSS (Fig. 8). The ED₅₀ (dose producing 50% relaxation) under these conditions was $7.1 \times 10^{-7}$ M in KCl contracted strips and $3.3 \times 10^{-8}$ M in norepinephrine-contracted strips. The same concentrations of nifedipine relaxed strips contracted by norepinephrine in Ca²⁺-free PSS and in Ca²⁺-free PSS with EGTA. After assessing the dose-response to nifedipine, the strips were washed several times and challenged again after 20 minutes. All responses were significantly depressed (Fig. 7, hatched bars) up to 3 hours after the experiments were terminated.

Discussion

The results of our in vivo studies indicate that both nifedipine and diltiazem are potent dilators of the intestinal circulation. Comparison of doses producing a 50% increase in blood flow to the ileum shows that nifedipine is about 7 times more potent than diltiazem on a molar basis. It appears that both agents dilate arteriolar resistance vessels in the intestinal circulation, while decreasing the tone
of large arteries as an additional effect. The latter effect has been suggested in the coronary circulation (Fleckenstein and Fleckenstein-Grün, 1977) but cannot alone account for such large increases in blood flow to the gut as were observed with these drugs. Vasodilation occurred mainly in the mucosal-submucosa with the calcium antagonists indicating that these compounds produce a redistribution of intestinal blood flow to the mucosal-submucosal compartment. This redistribution may have been related to the decrease in intestinal motor activity observed with these drugs, reflecting the important role of calcium in mediating contractile activity of both vascular and visceral smooth muscle (Anderson et al., 1972).

Dose-related increases in blood flow observed with the calcium antagonists were accompanied by proportional decreases in oxygen extraction across the intestinal circulation and resulted in no change in oxygen consumption by the gut. The lack of change in oxygen uptake suggests that the main micro-circulatory effect of these compounds, relaxation of arterioles, was not accompanied by any apparent relaxation of precapillary sphincters which regulate the nutrient circulation. The increased blood flow which bypasses the nutrient circulation thereby represents a functional arteriovenous shunting. It is also possible that Ca2+ antagonists depress intestinal function(s) and, therefore, reduce oxygen use by the gut, as has been shown in the myocardium (Fleckenstein, 1977; Fleckenstein and Fleckenstein-Grün, 1977). Were this the case, the decrease in oxygen utilization would nullify any effect of opening the precapillary sphincters. The more likely of these two explanations cannot be ascertained from our data.

Previous studies of the interactions of calcium antagonists with cardiac glycosides in the coronary and intestinal circulations showed that the antagonists appear to have different effects in the normal and digitalis-poisoned circulations.

In contrast to the high potency of calcium antagonists in the intestinal circulation, Ca2+ itself evoked very small constrictor effects in this vascular bed. Chou et al. (1963) reported a 10% increase in total intestinal resistance and a 20% increase in small-vessel resistance in response to an isotonic CaCl2 infusion at a rate of about 8 ml/min. The same group reported later that Ca2+ relaxed visceral smooth muscles but had no significant effect on intestinal resistance (Dabney et al., 1967). Infusion of CaCl2 at 300 μg/kg per min into the mesenteric artery was reported to decrease both blood flow and oxygen consumption by 12% (Pawlik et al., 1975). Maximal constriction obtained with CaCl2 in the present study corresponded to about a 20% decrease in blood flow. The dose-dependent decrease in blood flow was accompanied by an increase in oxygen extraction and no change in oxygen uptake, typical of a weak vasoconstrictor effect in this circulation. The highest dose of CaCl2 (1,000 μg/kg per min) produced, unexpectedly, a reproducible intestinal vasodilation accompanied by an increase in oxygen consumption. In additional experiments not reported here still higher doses of CaCl2 (2,000.0 and 5,000.0 μg/kg per min) prompted progressively greater dilator responses. We thought this vasodilation might be a function of the hyperosmolarity of the CaCl2 solution infused into the artery, since administration of hyperosmolar glucose or NaCl was shown to decrease vascular resistance in the feline intestinal circulation (Levine et al., 1978). In our study, however, solutions of NaCl or mannitol of the same osmolarity as the 1,000.0 μg/kg per min solution of CaCl2 infused i.a. did not change any circulatory or metabolic parameter. The vasodilator effect of the 1,000.0 μg/kg per min dose of calcium may be related to its effect on the membrane-bound Na+,K+-ATPase of the muscle cell. This enzyme is blocked by cardiac glycosides (Akerl, 1977), and this effect probably accounts for the vasoconstrictor effect of digitoxin in the intestinal circulation (Pawlik and Jacobson, 1974; Schwaiger et al., 1979). After blockade of Na+,K+-ATPase by digoxin, the dilator effect of the highest dose of CaCl2 was converted to a constrictor effect.

None of the doses of CaCl2 changed the distribution of intestinal blood flow, suggesting that vasocostriction or vasodilation was proportional in all intestinal layers. The three higher doses of CaCl2 also stimulated intestinal motility, a finding which is not in agreement with reports of others wherein a decrease in tone of intestinal musculature was observed with Ca2+ (Dabney et al., 1967). The stimulation of intestinal motility by Ca2+ is, however, consistent with the inhibitory effects on motility we observed with calcium antagonists and suggests that qualitative similarities exist between the role of Ca2+ in contractility of vascular and nonvascular smooth muscle. The suggestion that effects of ions on visceral smooth muscle may interfere with their action on vascular resistance (Chou et al., 1963; Dabney et al., 1967) appears unlikely, since a dose-related increase in intraluminal pressure was found with the three highest doses of CaCl2 whereas intestinal blood flow was first diminished and then augmented (at highest dose when the amplitude of intestinal contractions was highest). Our observations suggest different sensitivities of vascular and visceral smooth muscle to the increments of plasma Ca2+ concentrations.

Ca2+ may act through several mechanisms in vascular smooth muscles. First, a rise in extracellular Ca2+ increases the transmembrane concentration gradient, the membrane Ca2+ influx, and the intracellular concentration of the ion. This effect is not very pronounced, probably because much of the Ca2+ entering the cell is easily sequestered in intracellular stores before it can activate contractile proteins. Second, Ca2+ may stabilize the cell membrane or may stimulate Na+, K+-ATPase. Inhibition of vascular tone in vitro by supranormal extracel-
cular concentrations of Ca\(^{2+}\) has been shown previously (Winquist and Bevan, 1980). Whether this effect occurs over the entire range of concentrations and thus minimizes the direct constrictor effect or occurs only at very high concentrations remains to be established in studies of the direct effects of calcium on isolated enzymes.

Nifedipine completely blocked the circulatory effects of the highest contractile dose of calcium but only partially reduced the constrictor response of the intestinal circulation to norepinephrine. It is possible that reduction of norepinephrine-induced constriction reflects the ability of nifedipine to block increased Ca\(^{2+}\) influx which accounts in part for the constrictor action of the drug (Seidel and Bohr, 1971; Godfraind and Kaba, 1972; Bohr, 1978; Johansson, 1978; Meisher et al., 1980). Nifedipine is commonly believed to interfere with the slow inward current, i.e., transmembrane Ca\(^{2+}\) influx, or to reduce the number of slow channels (Fleckenstein, 1977; Fleckenstein and Fleckenstein-Grün, 1977; Bayer and Ehara, 1978; but an effect on intracellular calcium release has also been proposed (Church and Zsoter, 1980). Under in vitro conditions, nifedipine appeared to be a very effective relaxant of mesenteric arterial strips contracted with either norepinephrine or KCl and produced almost complete relaxation whether or not extracellular calcium was present in the medium. It is well established that KCl-induced contraction uses extracellular calcium whereas norepinephrine-mediated contraction depends on both extra- and intracellular Ca\(^{2+}\) (Hudgins and Weiss, 1968; Seidel and Bohr, 1971; Godfraind and Kaba, 1972; Bohr, 1978; Meisher et al., 1980) van Breeman et al., 1979). The ED\(_{50}\) of nifedipine fed norepinephrine-contracted strips was more than one order of magnitude lower than for KCl-contracted strips. This difference may mean that nifedipine relaxes vascular smooth muscle both by blocking Ca\(^{2+}\) influx and by preventing Ca\(^{2+}\) release from intracellular stores.

To exclude Ca\(^{2+}\) influx, we performed studies on the norepinephrine-nifedipine interaction after removing Ca\(^{2+}\) from the external medium. In both Ca\(^{2+}\)-free PSS and Ca\(^{2+}\)-free PSS with EGTA, norepinephrine still produced contraction, in contrast to KCl. This differential effect of Ca\(^{2+}\) removal on vascular smooth muscle from rat aorta was demonstrated previously by Hudgins and Weiss (1968), and our results confirm their findings. Contractions obtained with norepinephrine after removal of Ca\(^{2+}\) were not sustained. This finding is consistent with the suggestion that the tonic response to norepinephrine is due to increased uptake of external Ca\(^{2+}\) in contrast to the phasic (initial) response which depends upon release of Ca\(^{2+}\) from internal stores (Godfraind and Kaba, 1972). The difference probably is not discrete because phasic responses to norepinephrine in normal, Ca\(^{2+}\)-free and Ca\(^{2+}\)-free PSS with EGTA differ significantly. On the other hand, a part of the tonic response may also depend on intracellular Ca\(^{2+}\) release since the decrease in tension after norepinephrine was relatively slow in the absence of Ca\(^{2+}\). Addition of nifedipine in increasing concentrations accelerated the spontaneous decay of tension.

Nifedipine irreversibly blocked any subsequent responses to KCl or norepinephrine in any type of PSS. Thus, the drug interferes not only with KCl-induced contraction and the tonic response to norepinephrine, both of which depend mainly on extracellular Ca\(^{2+}\), but also with the phasic response to the catecholamine. In the absence of external Ca\(^{2+}\) (as is the case in Ca\(^{2+}\)-free PSS with EGTA), the phasic response depends entirely on intracellular Ca\(^{2+}\). It appears that Ca\(^{2+}\) antagonism by nifedipine involves blockade of both Ca\(^{2+}\) influx and Ca\(^{2+}\) release from intracellular sites. Increased Ca\(^{2+}\) influx is also possible as a mechanism of nifedipine-induced relaxation (Fleckenstein and Fleckenstein-Grün, 1977). Our results generally confirm the results of studies of Ca\(^{2+}\) fluxes under the influence of calcium antagonists (Church and Zsoter, 1980). The quantitative contribution of the preceding mechanisms to the vasodilator effects of these compounds cannot be established at this point.

In Ca\(^{2+}\)-free media, maximum relaxation of norepinephrine-contracted strips is much less than that of norepinephrine or KCl-contracted strips in the presence of Ca\(^{2+}\). Furthermore, at low concentrations of nifedipine, relaxation of strips contracted with norepinephrine in all types of PSS is similar to relaxation of strips contracted with KCl. These findings support the speculation that Ca\(^{2+}\) antagonists in low doses interact in a major way with the intracellular free Ca\(^{2+}\) pool. When the concentration of the drug is high, these drugs also affect membrane calcium flux, and produce additional relaxation. It is possible that studies of calcium fluxes in vascular smooth muscle might bear upon these speculations, although recent experiments (Church and Zsoter, 1980) using such techniques did not appear to yield definitive results.

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