Tonic regulation of vascular tone by nitric oxide and chloride ions in rat isolated small coronary arteries

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Graves, Jonathan E., Iain A. Greenwood, and William A. Large. Tonic regulation of vascular tone by nitric oxide and chloride ions in rat isolated small coronary arteries. Am J Physiol Heart Circ Physiol 279: H2604–H2611, 2000.—We have investigated the involvement of Cl− in regulating vascular tone in rat isolated coronary arteries mounted on a small vessel myograph. Mechanical removal of the endothelium or inhibition of nitric oxide (NO) synthase with Nω-nitro-L-arginine methyl ester (L-NAME, 10−4 M) led to contraction of rat coronary arteries, and these contractions were sensitive to nicardipine (10−6 M). This suggests that release of NO tonically inhibits a contractile mechanism that involves voltage-dependent Ca2+ channels. In arteries contracted with L-NAME, switching the bathing solution to physiological saline solution with a reduced Cl− concentration potentiated the contraction. DIDS (5 × 10−6–3 × 10−4 M) caused relaxation of L-NAME-induced tension (IC50 = 55 ± 10 μM), providing evidence for a role of Cl−. SITS (10−5–5 × 10−4 M) did not affect L-NAME-induced tension, suggesting that DIDS is not acting by inhibition of anion exchange. Mechanical removal of the endothelium led to contraction of arteries, which was sensitive to DIDS (IC50 = 50 ± 8 μM) and was not affected by SITS. This study suggests that, in rat coronary arteries, NO tonically suppresses a contractile mechanism that involves a Cl− conductance.

chloride channel; vascular smooth muscle

THE ENDOTHELIUM plays an important role in regulating vascular tone in many vascular beds, including the coronary circulation. In pressurized rat isolated small coronary arteries, nitric oxide (NO) modulates myogenic tone induced by increases in intravascular pressure (10). In the human coronary vascular bed, endothelium-derived NO contributes to metabolic vasodilation of large epicardial arteries (6), and mechanical removal of the endothelium increases intrinsic tone in the rat isolated coronary artery (23). This is of particular interest, inasmuch as removal of the endothelium or inhibition of NO synthase in arteries mounted as ring preparations from many other vascular beds produces little or no increase in basal tension (12, 16, 22, 28), although the effects of contractile agonists are potentiated (12, 16). This suggests that the mechanism producing contraction of coronary arteries in response to removal of the endothelium may not be present in the systemic circulation and is therefore a potential therapeutic target for a selective coronary vasodilator.

The potential importance of this observation is underlined by the well-documented finding that endothelial dysfunction is a feature of cardiovascular disease, including hypertension (7), diabetes (26), and atherosclerosis (19), all of which are risk factors for coronary artery disease. The association of endothelial dysfunction with increased risk of coronary artery disease suggests that coronary vasoconstriction due to reduction in tonic endothelium-derived NO may contribute to impaired myocardial perfusion.

Recent studies have suggested that the endothelium may regulate vascular tone via an effect on vascular smooth muscle Cl− channels (16). In these studies, norepinephrine-induced contractions of rat aorta were potentiated by reducing the Cl− concentration of the bathing solution, which suggests that outward movement of Cl− plays an important role in the contraction. This effect was potentiated in arteries treated with an NO synthase inhibitor or with the endothelium removed. In addition, low-Cl− solution also initiated contraction in unstimulated arteries without endothelium but did not cause contraction in arteries with an intact endothelium. These results are consistent with a role for membrane Cl− conductances as depolarizing mechanisms in vascular smooth muscle (18). Moreover, the above data suggest that an intrinsic Cl− mechanism is suppressed by NO.

We have therefore investigated how the coronary endothelium regulates intrinsic vascular tone in rat isolated small coronary arteries and explored the role of Cl− in mediating the contraction caused by removal of endothelium-derived NO.

METHODS

Male Wistar rats (250–350 g) were killed by cervical dislocation, and the heart was removed immediately and placed in cold buffer. Typically, two 1.5- to 2.0-mm sections of the septal artery were dissected from the interior wall of the...
right ventricle and mounted as ring preparations on a small vessel myograph within 1 h (n = 76, 285 ± 5 μm ID at 100 mmHg). The arteries were maintained at 37°C bubbled with 95% O2-5% CO2 in physiological saline solution (PSS) of the following composition (mM): 119 NaCl, 4.7 KCl, 2.5 CaCl2, 1.17 MgSO4, 25 NaHCO3, 1.18 NaH2PO4, 0.026 EDTA, and 6.0 glucose. Arteries were allowed to equilibrate for 1 h before estimation of the internal circumference that they would have at a passive transmural pressure of 100 mmHg in vivo (22). A series of stretches (4–6) were performed such that the calculated (from the Laplace equation) effective pressure exceeded 100 mmHg on the final stretch. From this, the arteries were set to a normalized diameter of 90% of that which they would have assumed in vivo. After a further 30-min equilibration, a series of three contractions to K-PSS (equimolar substitution of NaCl with KCl) was carried out, with the arteries being exposed to K-PSS for 2 min every 10 min.

Protocols

Effect of NO synthase inhibition and the role of Na+ and Cl−. To examine the influence of NO on vascular tone, 10−4 M Nω-nitro-L-arginine methyl ester (L-NAME) was added to the myograph bath, and the tension was recorded for up to 3 h. The contribution of Cl− and Na+ to the contraction elicited by L-NAME was investigated by the use of low-Cl− and low-Na+ PSS solutions. After contraction to L-NAME, the solution in the myograph bath was washed to either PSS or to low-Cl− PSS (equimolar substitution of NaCl with sodium isothionate) or low-Na+ PSS (equimolar substitution of NaCl with choline chloride + 10−6 M atropine or equimolar substitution of NaCl with N-methyl-d-glucamine chloride), and the change in tension was recorded for 5 min in the continued presence of L-NAME before the solution was washed to PSS and L-NAME (10−4 M).

Effect of Cl− channel blockers on voltage-dependent Ca2+ channels. To examine the effect of Cl− channel blockers on voltage-dependent Ca2+ channels (VDCCs), cumulative concentration-response curves to Cl− channel blockers were carried out on coronary arteries precontracted with 45 mM K+. After a stable contraction to K+ was established, Cl− channel blockers were added in increasing concentrations every 4 min. Drugs that did not affect the K+ spasm at concentrations at which they had previously been shown to affect Cl− channels in electrophysiological studies were then tested on the contraction to L-NAME.

Effect of Cl− channel blockers on L-NAME-induced tension. To investigate the role of Cl− channels on the contraction to L-NAME, cumulative concentration-response curves to Cl− channel blockers were carried out in arteries contracted with L-NAME. Increasing concentrations of DIDS and SITS were added every 4 min. Inasmuch as the level of precontraction can affect the response to vasodilators, only arteries that contracted >0.5 mN/mm were used to examine the effects of the stilbene derivatives.

Effect of endothelial removal on vascular tone and the effect of Cl− channel blockers. Two sections of the same septal artery were mounted and contracted with U-46619 (10−7 M) and challenged with ACh (10−7–10−5 M). After washout, the endothelium was removed from one artery by careful rubbing with a human forearm hair while the artery was still mounted on the myograph; the other artery was used as a control. The arteries were then contracted with U-46619 (10−7 M) and challenged with ACh, and a <10% relaxation to ACh was taken as evidence of endothelial removal. After washout, the arteries were left until they had contracted >0.5 mN/mm. Subsequently, a cumulative concentration response to DIDS (5 × 10−6–3 × 10−4 M) was carried out, with increasing concentrations of DIDS being added every 4 min.

Effect of Cl− transport inhibitors on L-NAME-induced tension. The effect of the K+−Na+−2Cl− cotransporter inhibitor bumetanide (10−5 M) was investigated on arteries precontracted with L-NAME. After contraction to L-NAME, arteries were exposed for 30 min to bumetanide, and tension was recorded. SITS (5 × 10−4 M) was then added in the continued presence of bumetanide, and tension was recorded after a further 30 min.

Drugs

DIDS, SITS, tamoxifen, 9,11-dideoxy-11α,9α-epoxymethano-prostaglandin F2α (U-46619), ACh hydrochloride, niflumic acid, 5-nitro-2-(3-phenylpropylamino)benzoic acid, L-NAME, and nicardipine were obtained from Sigma Chemical (Poole, UK). IAA-94 was obtained from Research Biochemicals (Natick, MA).

RESULTS

Effect of Inhibition of NO Synthase on Tension of Rat Septal Arteries

Incubation with the NO synthase inhibitor L-NAME caused contraction of >0.50 mN/mm in 70% of arteries and some contraction in all arteries. A representative trace of the effect of L-NAME is shown in Fig. 1A, and
the contraction to l-NAME was well maintained for up to 3 h. In 44 arteries, l-NAME induced a contraction of $1.10 \pm 0.12$ mN/mm. The contraction to l-NAME was unaffected by $0.1-0.5\%$ DMSO, which was used as a vehicle for drugs, but was greatly attenuated $(95 \pm 3\%, n = 5)$ by the voltage-gated Ca$^{2+}$ channel blocker nicardipine $(10^{-6} \text{M})$. In three arteries, removal of the endothelium caused contraction of $0.76 \pm 0.11$ mN/mm, and this contraction was abolished by nicardipine $(10^{-6} \text{M})$. A representative trace of the effect of nicardipine is shown in Fig. 1B. These data suggest that inhibition of NO synthase and removal of the endothelium initiate contraction by a mechanism that involves Ca$^{2+}$ entry through VDCCs.

**Effect of Low-Cl$^{-}$ Solution on Basal and l-NAME-Induced Tone**

VDCCs are opened by membrane depolarization, and therefore it is possible that NO suppresses a depolarizing mechanism. In smooth muscle the ionic mechanisms most likely to give rise to a depolarization are efflux of Cl$^{-}$ and influx of Na$^{+}$. Replacing the Cl$^{-}$ with a less-permeant anion (isethionate) will increase the outward electrochemical gradient for Cl$^{-}$ and thus potentiate contraction if it is dependent on the outward movement of Cl$^{-}$. In six arteries, washout to low-Cl$^{-}$ PSS had only a small effect on tension on unstimulated arteries compared with washout to normal PSS (Fig. 2A). In contrast, in the same six arteries, when contraction had been induced by l-NAME (contraction $= 0.99 \pm 0.17$ mN/mm), substitution of PSS by low-Cl$^{-}$ PSS led to a potentiation of the contraction (Fig. 2B). These data are consistent with the proposal that the contraction induced by l-NAME involves the outward movement of Cl$^{-}$.

**Effect of Low-Na$^{+}$ Solutions on l-NAME-Induced Tone**

Depolarization of vascular smooth muscle can also occur by the opening of nonspecific cation channels and subsequent Na$^{+}$ influx (3). Replacement of the Na$^{+}$ by a relatively impermeant cation in the bathing solution should cause relaxation of the vascular smooth muscle if this mechanism is involved in the contraction to l-NAME. In four arteries treated with l-NAME (contraction $= 1.25 \pm 0.30$ mN/mm), replacement of PSS by low-Na$^{+}$ PSS (N-methyl-D-glucamine chloride substitution) gave an initial relaxation that was not significantly different from wash to normal PSS (Fig. 3), and this was followed by a substantial contraction. In four separate arteries treated with l-NAME (contraction $= 0.88 \pm 0.20$ mN/mm), wash to low-Na$^{+}$ PSS (choline chloride substitution) also led to an immediate and profound contraction (Fig. 3). We are uncertain as to the mechanism of the contraction in low-Na$^{+}$ PSS, but these data clearly suggest that influx of Na$^{+}$ is not responsible for the contraction to l-NAME.

![Fig. 2. Effect of low-Cl$^{-}$ solution on tension in rat isolated small coronary arteries mounted on a small vessel myograph before and after contraction with l-NAME. Change in tension was measured every 1 min for 5 min after bathing solution was switched. A: effect of replacement of physiological saline solution (PSS) with low-Cl$^{-}$ PSS on basal tension of rat isolated coronary arteries before addition of l-NAME. B: effect of replacement of PSS with low-Cl$^{-}$ PSS on tension of rat isolated coronary arteries after contraction to l-NAME. Each point is mean ± SE of 6 arteries.](http://ajpheart.physiology.org/ by 10.220.33.1 on June 29, 2017)
Effect of Cl⁻ Current Inhibitors on K⁺-Induced Tone

In the next series of experiments, we investigated the effects of agents that have been shown to inhibit various Cl⁻ conductances in electrophysiological experiments. Drugs that have been shown to inhibit Cl⁻ channels in electrophysiological experiments can have other effects that would also lead to vasodilation in functional studies, namely, inhibition of VDCCs and opening of K⁺ channels (5, 13). To investigate the effects of Cl⁻ channel blockers on VDCCs, we examined their effects on the nicardipine-sensitive contraction induced by 45 mM K-PSS in arteries with an intact endothelium. The stilbene derivatives DIDS and SITS did not cause relaxation of tension induced by 45 mM K-PSS and, therefore, did not block VDCCs in this preparation. Tension remaining after exposure of arteries precontracted with 45 mM K⁺ to DIDS (3 × 10⁻⁴ M) was 101 ± 7% (n = 4). A representative trace of the effects of DIDS is shown in Fig. 4A. In contrast, all the other Cl⁻ channel blockers tested caused relaxation of 45 mM K-PSS-induced tension and included tamoxifen (10⁻⁵ M, 78 ± 10%, n = 3), 5-nitro-2-(3-phenylpropylamino)benzoic acid (3 × 10⁻⁶ M, 61 ± 12%, n = 4), IAA-94 (10⁻⁴ M, 58 ± 11%, n = 4), and niflumic acid (2 × 10⁻⁴ M, 40 ± 9%, n = 4). Therefore, we tested the stilbene derivatives DIDS and SITS against the contraction produced by L-NAME or endothelial removal.

The K⁺ channel opener levcromakalim (10⁻⁶–10⁻⁵ M) induced relaxation in rat isolated coronary arteries contracted with 45 mM K-PSS, and the maximum relaxation to 10⁻⁵ M was 73 ± 3% (n = 5); a representative trace is shown in Fig. 4B. Levcromakalim did not cause relaxation of tension in arteries contracted with 60 mM K-PSS. These data suggest that levcromakalim is causing relaxation of arteries contracted by 45 mM K⁺ by opening K⁺ channels, and therefore the observation that DIDS did not cause relaxation of 45 mM K-PSS-induced tension indicates that the agent is not acting as a K⁺ channel opener.

Effect of Stilbene Cl⁻ Channel Blockers on L-NAME-Induced Tone

Addition of DIDS (5 × 10⁻⁶–3 × 10⁻⁴ M) caused concentration-dependent relaxation of coronary arteries contracted by addition of L-NAME (contraction = 1.25 ± 0.28 mN/mm, n = 8); a representative trace and a summary of the data are shown in Fig. 5. The IC₅₀ for DIDS against L-NAME was 55 ± 10 μM (n = 8). In coronary arteries precontracted with U-46619 (contraction = 1.40 ± 0.14 mN/mm, n = 5), DIDS elicited a relaxation but was markedly less potent than against the L-NAME-induced contraction. In a separate series of six arteries, L-NAME caused a contraction of 0.89 ± 0.12 mN/mm, and addition of the stilbene derivative SITS (10⁻⁵–5 × 10⁻⁴ M) did not cause relaxation. The percentage of the initial tension remaining after 5 × 10⁻⁴ M SITS was 107 ± 14%.
Effect of Mechanical Removal of the Endothelium

The maximum relaxation to ACh was 63 ± 5% when the artery was precontracted with U-46619 before mechanical removal of the endothelium, and after the endothelium was removed, the maximum relaxation was reduced to 16 ± 3%. A representative trace showing the contractile effect of endothelial removal and the subsequent relaxation to DIDS (5–300 μM) is shown in Fig. 6A. In this experiment, after washout of DIDS, the artery contracted again, and a single dose of SITS (500 μM) was added that produced only a small relaxation. Inasmuch as SITS would be expected to cause a substantial blockade of the anion exchanger, the above evidence suggests that the DIDS-induced relaxation is not due to inhibition of this mechanism. All five arteries subjected to mechanical removal of the endothelium contracted (mean contraction = 0.64 ± 0.05 mN/mm after 52 ± 5 min; mean contraction in 5 control arteries with intact endothelium = 0.01 ± 0.04 mN/mm). A concentration response to DIDS was carried out, and the mean results are shown in Fig. 6B. DIDS caused a concentration-dependent relaxation in endothelium-denuded arteries, with a maximum relaxation of −0.80 ± 0.11 mN/mm, slightly below the original baseline. The IC50 for DIDS was 50 ± 8 μM (n = 5). The presence of some intrinsic tone that was sensitive to DIDS in these experiments was confirmed by the slight relaxation of arteries with an intact endothelium of 0.10 ± 0.05 mN/mm.

Effect of Cl− Transport Inhibitors on L-NAME-Induced Tension

We investigated the effect of inhibitors of the Na+–K+–2Cl− cotransporter (bumetanide) and Cl−/HCO3− exchanger (SITS) that would be expected to reduce the outward Cl− gradient. L-NAME contracted four arteries (0.54 ± 0.05, n = 4), and addition of bumetanide (10 μM) caused a small contraction that was 16 ± 8% of the initial tension after 5 min (Fig. 7). This was followed by a relaxation of 25 ± 4% of the initial tension after 30 min. Addition of SITS (500 μM) caused a further relaxation of 78 ± 4% of the initial tension.

DISCUSSION

The major finding of this study is that, in rat isolated small coronary arteries, endothelium-derived NO pro-
vides a tonic inhibition of an intrinsic contractile mechanism that involves Cl⁻. The contractile effects of L-NAME and removal of the endothelium confirm the contribution of NO from the endothelium as a tonic vasodilator influence. The contraction is mediated by entry of Ca²⁺ into the vascular smooth muscle via VDCCs, inasmuch as the contractions are sensitive to nicardipine. This suggests that, in arteries with a functioning endothelium, NO suppresses an intrinsic depolarizing mechanism and subsequent removal of NO produces depolarization of the smooth muscle cells to open VDCCs to cause contraction. Future studies simultaneously measuring tension by means of the myograph and membrane potential by microelectrode will be carried out to confirm the central role of a depolarizing mechanism.

There are three potential depolarizing influences involving ion channels in vascular smooth muscle: opening of Cl⁻ channels leading to Cl⁻ efflux, opening of nonspecific cation channels leading to Na⁺ influx, and closing of K⁺ channels. The potentiation of the contraction to L-NAME by reduction of extracellular Cl⁻ is consistent with an outward movement of Cl⁻ through a Cl⁻ channel being responsible for the depolarization. If a nonspecific cation channel were mediating the depolarization, reduction of extracellular Na⁺ would be expected to decrease depolarization and contraction, whereas this procedure produced a contraction. This suggests that the contraction induced by L-NAME is not mediated by a nonspecific cation channel. However, a degree of caution is necessary in interpreting the data from ion substitution experiments, since we do not have precise information on the intracellular ion concentrations. In addition, other ion transport mechanisms may be affected. There is evidence for NO opening K⁺ channels to cause hyperpolarization (1, 2), and we cannot rule out the possibility that removal of a hyperpolarizing K⁺ influx could play a role in the contraction to L-NAME. Nevertheless, the data imply that when NO is removed, the smooth muscle cells of the rat coronary circulation depolarize sufficiently to open VDCCs to produce contraction. This is clearly different from most systemic arteries, where inhibition of NO synthesis or mechanical removal of the endothelium does not evoke contraction. A recent report demonstrated that the endothelium inhibits anion channel-dependent contractions of rat aortic rings elicited by substitution of the more-permeable anion I⁻ for Cl⁻ (17). In contrast to our study, removal of the endothelium alone in the rat aorta did not lead to significant contraction, and the endothelial factor involved was not NO.

Relaxation by DIDS of arteries contracted by L-NAME or removal of the endothelium is further evidence for a role of Cl⁻ in mediating the contraction. The relaxation to DIDS is observed in endothelium-denuded vessels and is therefore due to a direct effect on the vascular smooth muscle. We have demonstrated that DIDS is not acting as a VDCC blocker. We also attempted to examine whether DIDS relaxed the artery by opening of K⁺ channels. DIDS did not relax the contraction to 45 mM K⁺, which was inhibited by the K⁺ channel opener levcromakalim. Levcromakalim did not inhibit the contraction produced by 60 mM K⁺. However, without membrane potential measurement, this conclusion is tentative, inasmuch as K⁺ equilibrium potential, and presumably membrane potential, should be around −30 mV, and levcromakalim may not be able to hyperpolarize the smooth muscle under these conditions.

The most likely explanation for the vasodilator action of DIDS is via its effects on mechanisms involving Cl⁻. In addition to blockade of Cl⁻ channels, the stilbene derivatives also block the Cl⁻/HCO₃⁻ exchanger mechanism, which may be involved in maintaining intracellular Cl⁻ concentration. Blockade of this mechanism could induce relaxation by reducing the Cl⁻ electrochemical gradient that is responsible for the depolarizing influence of opening Cl⁻ channels. However, SITS, which has a potency similar to DIDS on the Cl⁻/HCO₃⁻ exchanger (4, 9), did not relax coronary arteries when added on its own. However, bumetanide, an inhibitor of the Na⁺-K⁺-2Cl⁻ cotransporter, produced a relaxation of the L-NAME-induced contraction after 30 min. Subsequent addition of SITS in the con-
continued presence of bumetanide produced a substantial relaxation. This result suggests that both Cl− transport mechanisms are able to maintain an outward Cl− electrochemical gradient in these arteries and that the contraction to L-NAME is dependent on this electrochemical gradient being maintained. The vasodilator action of DIDS is not likely to be due to inhibition of inward Cl− transport systems.

Other potential targets for DIDS are membrane Cl− conductances, which produce depolarization in vascular smooth muscle. Two Cl− currents have been identified in vascular smooth muscle: the Ca2+-activated Cl− current \( I_{\text{Cl(Ca)}} \) and the swell-activated Cl− current \( I_{\text{Cl(swell)}} \). The IC50 for DIDS against \( I_{\text{Cl(Ca)}} \) is 200–700 μM (18), similar to the concentration (150 μM) required to cause 50% relaxation of coronary arteries contracted with U-46619. Therefore, it is possible that U-46619 activates \( I_{\text{Cl(Ca)}} \) to produce contraction in this tissue. Previously, it was suggested that \( I_{\text{Cl(Ca)}} \) represents a depolarizing mechanism for agonist-induced contraction in blood vessels (18). DIDS is an effective inhibitor of \( I_{\text{Cl(swell)}} \) with an IC50 of 21 μM in rabbit isolated portal vein smooth muscle cells (14), which is similar to the IC50 of 55 μM estimated for DIDS against L-NAME-induced contraction, and an IC50 of 50 μM for DIDS against the contraction to endothelial removal in the present study. In contrast, SITS has been shown to be much less potent than DIDS against \( I_{\text{Cl(swell)}} \) in canine colonic myocytes (5). It is worth noting that the inhibitory effect of DIDS against the contraction to L-NAME was much more rapid than the relaxation induced by bumetanide + SITS. These results are consistent with DIDS acting as a channel blocker (14) and bumetanide and SITS as transport inhibitors. Preliminary studies show that NO inhibits \( I_{\text{Cl(swell)}} \) in rabbit isolated portal vein smooth muscle cells (8). Consequently, it is possible that \( I_{\text{Cl(swell)}} \) may represent the depolarizing mechanism that is suppressed by NO in rat isolated coronary arteries. However, the precise identification of which Cl− channels may be involved will require single-cell electrophysiological studies.

The mechanism underlying the contraction to low Na+ (25 mM) is interesting and appears to involve depolarization of the vascular smooth muscle, inasmuch as the contraction was sensitive to nicardipine (J. Graves, unpublished observations). Na+−K+−ATPase has been reported to be inhibited by low extracellular Na+ (<50 mM), and inhibition of this electrogenic mechanism would cause depolarization and thus contraction. The contraction to low Na+ is of interest, inasmuch as it presents another feature of these coronary arteries that is very different from that previously reported for systemic arteries. It has been reported that rat isolated mesenteric resistance arteries do not contract to low-Na+ solutions unless they are pre-treated with ouabain (20). In addition, low-Na+ solutions potentiate myogenic tone in arteries and veins, although the low-Na+ solutions used in this study may have had reduced Cl− content (15).

Interestingly, human epicardial arteries also contract when treated with NO synthase inhibitors (27), and this raises the possibility that a similar mechanism exists in the human coronary circulation. Spontaneous contractile activity of human isolated coronary arteries that is sensitive to Ca2+ channel antagonists has also been described (25). This intrinsic activity and contraction to disruption of the NO pathway is not seen in most small systemic arteries. Thus this Cl− mechanism, if present in humans, may provide a potential therapeutic target for selective vasodilation of coronary arteries. Since this contractile mechanism may be prominent in arteries with a damaged endothelium, agents targeting this mechanism may act more potently on diseased arteries and thus avoid cardiac steal.

Conclusion

We have provided evidence that a mechanism involving Cl−, possibly a Cl− conductance, is involved in the contraction of rat coronary arteries produced by removal of endothelium-derived NO. This mechanism may be of great importance in cardiovascular disease associated with disturbances in the coronary circulation and is a novel target for therapy.

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REFERENCES


