Nitroglycerin-mediated vasorelaxation is modulated by endothelial calcium-activated potassium channels

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Abstract

Objective: Recent in vitro data suggest, large conductance calcium-activated K channels (BK) modulate the vascular response to nitric oxide (NO). The in vivo implications and the characteristics of this interaction are not clear. This study firstly investigates whether modulation of BK affects the vascular response to nitroglycerin (NTG)-derived NO in vivo and in the isolated heart and secondly examines the influence of endothelial BK on NTG-mediated vasodilation in vitro. Methods: The hypotensive effect of NTG was measured in conscious, chronically catheterized rats during i.v. infusions of iberiotoxin (IbTX, a selective inhibitor of BK) or placebo. Similarly, NTG-induced flow-changes in the isolated perfused rat heart were examined before and after IbTX treatment (0.1 μM). Concentration-relaxation curves to NTG in the presence of various K channel modulating agents were performed in vitro on porcine coronary arteries with and without intact endothelium. Results: I.v. infusion of IbTX reduced the in vivo hypotensive effect of NTG by 55% (before IbTX: 32.0 ± 3.0 mmHg, vs. after IbTX: 14.5 ± 3.2 mmHg, P < 0.05) and nearly abolished NTG-induced increase in coronary flow in the isolated perfused heart (P < 0.05). In vitro, this effect depended on an intact endothelium (endothelium intact segments; NTG: pD2 = 5.8 ± 0.1, Emax = 97.6 ± 3.2% vs. NTG+IbTX: pD2 = 4.9 ± 0.2, Emax = 49.7 ± 6.2%, P < 0.05; endothelium denuded segments; NTG: pD2 = 6.9 ± 0.2, Emax = 104.0 ± 1.4% vs. NTG+IbTX: pD2 = 6.7 ± 0.1, Emax = 100 ± 1.2%, P > 0.05). Conclusion: The results suggest, that modulation of endothelial BK significantly affects NTG-induced vasorelaxation in vitro, in the isolated perfused heart and in vivo. © 1999 Elsevier Science B.V. All rights reserved.

Keywords: Nitroglycerin; Nitric oxide; Endothelium; Potassium channels; iberiotoxin

1. Introduction

Nitric oxide (NO) is an important regulator of vascular smooth muscle tone. It is produced either through the endogenous L-arginine–citrulline–NO pathway or from pharmacological nitrovasodilators like nitroglycerin (NTG). NO-mediated vasorelaxation involves guanylate cyclase mediated changes in cyclic guanosine monophosphate (cGMP)-levels in the smooth muscle cells [1]. Recent data from patch-clamp experiments suggest that large conductance calcium-activated K’ channels (BKCa) may be activated via the NO-cGMP pathway [2] and that BKCa modulate the vasodilator response to both exogenous nitrovasodilators and endogenous receptor-mediated NO release (acetylcholine) in isolated arteries [3,4]. Currently, the in vivo significance of this interaction between NO and BKCa is not clear.

BKCa have been identified in both vascular smooth muscle and endothelial cells and constitute a subgroup among many different types of K’ channels. BKCa serve as a negative feed-back mechanism limiting the depolarizing and Ca2+ increasing effects of vasoconstrictors. Opening of BKCa will allow K’ flux out of the cell leading to a change in the membrane-potential in a hyperpolarizing direction and induce vasodilation.

Interestingly, pharmacological hyperpolarization may augment NO-mediated vasorelaxation through diminished production of superoxide anions (O2•−) in the vascular endothelium. This finding suggests a possible endothelium-dependent regulatory mechanism of NO action, involving
endothelial BK_{Ca}, endothelial O₂ production and thus the vascular bioavailability of NO [5].

In this study we sought to investigate 1) whether the vascular response to NTG-derived NO in vivo and in the isolated perfused heart is affected by BK_{Ca} modulation and 2) whether the vascular endothelium is likely to play a role in the NO-mediated activation of BK_{Ca} which occurs in vitro.

2. Methods

All studies conform with the Guide for the Care and Use of Laboratory Animals published by the US National Institutes of Health (NIH publication No. 85-23, revised 1996).

2.1. In vivo study

The in vivo effect of BK_{Ca} blockade on the vasodilator action of NTG was studied in conscious, chronically catheterized, male, Wistar rats (250–290 g). After catheter implantation in the ascending aorta and jugular vein, the rats were allowed to recover (5–7 days) until they had gained their preoperative weight and appeared healthy.

Arterial blood pressure was measured continuously by a pressure transducer (Baxter Corp., Holland) connected to the arterial catheter (medical-grade Tygon catheter). Tracings were recorded by Maclab System for computerised data recording and analysis. This animal model has previously been described in detail [6].

2.1.1. In vivo study protocol

Two groups of six rats were studied. One group of animals received an infusion of iberiotoxin (IbTX; 0.1 mg kg⁻¹ i.v. over 5 min) and the control group received an infusion of IbTX vehicle (0.9% NaCl). IbTX is a highly selective inhibitor of BK_{Ca} [7]. The blood pressure lowering effect of NTG (20 mg kg⁻¹ i.v. over 1 min) was tested one hour before and during the last minute of IbTX/vehicle infusion.

2.2. Isolated perfused rat hearts

Male Wistar rats (250–280 g) were anaesthetized with pentobarbital (100 mg kg⁻¹ i.p.) and then ventilated through a tracheal cannula using a rodent respirator (Ugo Basile, type 7025, Italy). After heparinization (1000 IU kg⁻¹ i.a.), the chest was opened and the heart perfused in situ through a cannula inserted into the ascending thoracic aorta. The perfused heart was then excised and mounted in a Langendorff apparatus (type 830, Hugo Sachs Electronic, Germany). Hearts were electrically paced at a heart rate of 300 min⁻¹ and the perfusion pressure was kept constant at 80 mmHg. Coronary flow rate was measured continuously by an electromagnetic flowmeterhead. The perfusion liquid was a modified Krebs-Henseleit solution (pH 7.4, 37°C, continuously aerated with a mixture of 95% O₂ and 5% CO₂) with the following composition in mM: NaCl 118.0, KCl 4.6, CaCl₂ 2.5, MgSO₄ 1.15, NaHCO₃ 24.9, KH₂PO₄ 1.15, glucose 5.5, pyruvate 2.0. Drugs were infused into the aortic perfusion line using adjustable precision syringe pumps. The hearts were allowed to equilibrate for 30 min.

2.2.1. Study protocol

The coronary vasodilator effect of NTG was measured by the construction of concentration-response curves (0.1–1000 μM) for both NTG and NTG-solvent (n=6 in each group). The first concentration of NTG or NTG-solvent was infused for 3 min and the following concentrations were infused with a standard 7 min intervention wash-out period. Based on the concentration-response curve, NTG 50 μM was used in the subsequent experiments, where changes in coronary flow to NTG were examined before (response=100%) and during infusion of IbTX (0.1 μM) (n=5). The IbTX-infusion commenced 5 min before the second NTG infusion.

The second part of the study protocol was repeated on perfused hearts from rats (n=6), which received an intravenous bolus infusion of PEG–SOD (30 000 units/kg) 16–24 hours before study [8]. The infusion was given in a catheter placed in the jugular vein 5–7 days in advance. In addition PEG–SOD (150 μg/ml) was added to the perfusion liquid. After treatment with PEG–SOD, the response to 50 μM NTG was studied before (response=100%) and during infusion of IbTX as described above.

2.3. Isolated coronary arteries

The left anterior descending coronary artery from male Wistar rats (400–450 g) and from fresh porcine hearts was cleaned of adhering tissue and cut into ring segments, 1.5 mm long. Each arterial segment was mounted in a myograph either by the insertion of a stainless-steel wire (rat experiments) or two fine stainless steel pins (porcine experiments) into the vessel lumen. The myograph systems have previously been described in detail [9,10]. Six myographs were used, allowing six arterial preparations to be studied simultaneously. Transducer signals were amplified and displayed on an 8-channel Graphitec arraycorder (Graphitec Corp., Japan). Vascular preparations were submerged in 5 ml tissue baths containing Krebs solution (composition in mM: NaCl 118.0, KCl 4.6, CaCl₂ 2.5, MgSO₄ 1.15, NaHCO₃ 24.9, KH₂PO₄ 1.15, glucose 5.5) at 37°C and aerated with a mixture of 95% O₂ and 5% CO₂ (pH=7.4). In experiments involving high K⁺, 30 mM and 80 mM isoosmolar K⁺ Krebs solutions were prepared by substituting equimolar concentrations of NaCl with KCl. Arterial segments were stretched to a passive tension of 0.5 g (rats) or 2.0 g (pigs) (optimal contraction in
response to K⁺-depolarisation) and allowed to stabilize for about 1 hour before the addition of drugs. Indomethacin (3 μM) was added to all the organ-baths in all experiments to block the effects of endogenous prostaglandin synthesis. In addition, experiments were carried out with BQ-123 (1 μM) to block the effect of endothelin and N-Nitro-l-Arginine (l-NA, 100 μM) to inhibit the endogenous NO formation. Unless otherwise stated, experiments were carried out in both endothelium-intact and endothelium-denuded vessel segments. The endothelium was carefully removed by gently rubbing the luminal surface of the vessel with a stick made of wood. The presence or absence of a functionally intact endothelium was examined by recording the response to the endothelium-dependent vasodilator substance P (0.1 μM) added to arteries precontracted with PGF₂α (10 μM).

2.3.1. Study protocols

The influence of K⁺ channel manipulation on the vasorelaxant response to NTG was examined in various individual experiments (n=6–10 in each experimental group).

2.3.2. Effect of K⁺ channel blockade

Vascular ring segments precontracted by PGF₂α (10 μM) were used to examine the possible effect of selected K⁺ channel blockers on the vasorelaxation mediated by NTG (0.001–30 μM). The vasorelaxant effect of NTG was examined after preincubation with: iberiotoxin (IbTX, 0.1 μM), a highly selective inhibitor of BKCa; tetraethylammonium chloride (TEA, 100 μM), a blocker of BKCa, but at higher concentrations a non-specific K⁺ channel blocker; glibenclamide (1 μM) a blocker of ATP-sensitive K⁺ channels (K₅, ATP) and apamin (0.1 μM), a selective blocker of small conductance-activated K⁺ channels.

Since the results of the BKCa blockade experiments confirmed, that the effect of IbTX was qualitatively similar in both animal species, only porcine coronary artery preparations were used in the experiments described below.

2.3.3. Potassium channel opening characteristics of NTG

Drugs acting by K⁺ channel opening preferentially relax arteries precontracted by moderately raised extracellular K⁺ compared with those contracted by highly elevated K⁺. To investigate whether NTG possesses potassium channel opener characteristics, the effect of NTG (0.001–30 μM) was examined in vessels precontracted either by 30 mM K⁺ or 80 mM K⁺.

2.3.4. Effect of sGC inhibition

We tested the effect of NS2028, a new specific blocker of the soluble guanylate cyclase [11]. Dose-response experiments for NTG were performed after incubation with NS2028 (1 μM) alone or in combination with IbTX (0.1 μM).

2.3.5. Effect of IbTX on nimodipine and sodium nitroprusside (snp) induced vasorelaxation

Concentration-relaxation control experiments with or without IbTX were performed in endothelium intact segments using nimodipine (an L-type calcium entry blocker with a mechanism of action different from K⁺ channel opening, 10⁻¹²–3×10⁻⁶ M) and sodium nitroprusside (another nitrovasodilator, 10⁻⁸–3×10⁻⁵ M).

3. Data analysis and statistics

In the in vivo model, mean arterial blood pressure (MAP) was registered in mmHg in the following way: diastolic pressure+(systolic−diastolic pressure)/3. Vasorelaxant responses are expressed as % relaxation relative to the level of preconstriction in isolated coronary arteries. Values of EC50 are given as pD₂ values (−log EC₅₀) estimated by fitting the combined dose-response relaxation curves to the 3-parameter logistic equation (Hill-equation) using non-linear regression analysis. Comparisons between experimental groups were done by paired and unpaired Student’s t tests as appropriate. All data are presented as means±SEM. Statistical significance was assumed at P<0.05.

4. Drugs

Nitroglycerin (DAK, Denmark), prostaglandin F₂α (Dinoprost trometamol, Upjohn, Belgium), nimodipine (Bayer, Germany), indomethacin, iberiotoxin, tetraethylammonium chloride, glibenclamide, apamin, substance P, sodium nitroprusside, superoxide dismutase covalently linked to polyethylene glycol (PEG-SOD), N-Nitro-l-Arginine (l-NA) (Sigma, USA), NS2028 (NeuroSearch, Denmark) and BQ-123 (Calbiochem, Germany). Indomethacin was dissolved in 5% sodium hydrogen carbonate.

5. Results

5.1. In vivo study

Mean arterial blood pressure (MAP=112.3±2.9 mmHg; n=6 for the IbTX-group and MAP=110.8±8.9 mmHg; n=4 for the solvent-group) was similar in both groups of animals before start of IbTX or solvent infusion. Infusion of IbTX did not affect MAP (MAP during infusion of IbTX/solvent; 102.2±2.6 vs. 107.2±3.3 mmHg, P>0.05). Infusion of IbTX, however, significantly (P<0.005) re-
duced the blood pressure lowering effect of NTG by 55% (before IbTX: 32.0±3.0 mmHg vs. after IbTX: 14.5±3.2 mmHg), suggesting that BK<sub>ca</sub> blockade significantly attenuates the in vivo vasodilatory response to NTG-derived NO (Fig. 1A). No change in the response to NTG was observed in the control group (before IbTX-solvent 30.3±6.6 mmHg vs. after IbTX-solvent 25.3±4.7 mmHg).

5.2. Isolated perfused rat hearts

In isolated perfused rat hearts, the effect of NTG was reproducible and NTG concentration-dependently increased coronary flow (data not shown). The maximal increase in coronary flow rate was 33.9±5.6% at 100 μM (n=5). In the experiment, examining the effect of NTG (50 μM) before and after IbTX (0.1 μM), the NTG-induced increase in coronary flow was reduced by 76.9±5.9% after infusion of IbTX (P<0.05) (Fig. 1B). Interestingly, IbTX only decreased the effect of NTG by 40.3±9.0% after pretreatment with PEG-SOD, suggesting that scavenging of reactive oxygen radicals diminish the hemodynamic effect of BK<sub>ca</sub> blockade on NTG-mediated vasodilation (Fig. 5). IbTX per se did not change the basal coronary flow rate (8.7±0.9 ml/min before, 7.5±1.0 ml/min after IbTX, P>0.05).

5.3. Isolated coronary arteries

5.3.1. Effect of K<sup>+</sup> channel blockade

NTG produced concentration-dependent relaxation of porcine endothelium-intact preparations precontracted by PGF<sub>2α</sub> (10 μM) (P<sub>D</sub>50 = 5.80±0.05, E<sub>max</sub> = 97.6±3.2%) (Fig. 2A and Table 1). The response to NTG was markedly inhibited by IbTX in both rat (NTG: P<sub>D</sub>50 = 7.33±0.1, E<sub>max</sub> = 89.2±2.4%; NTG+IbTX: P<sub>D</sub>50 = 6.55±0.2, E<sub>max</sub> = 33.1±1.9%, P<0.05) (Fig. 1C) and porcine coronary arteries (Fig. 2A and Table 1). Also TEA produced a significant inhibition of the vasorelaxant effect of NTG, whereas glibenclamide and apamin failed to influence NTG-induced vasorelaxation (Table 1). The effect of IbTX on NTG-mediated vasorelaxation was not affected by inhibition of endogenous NO formation (L-NA) or endothelin-receptor blockade using BQ-123 (data not shown). Changes in the precontraction level per se did not affect the concentration-relaxation curve for NTG (PGF<sub>2α</sub> 3 μM; precontraction = 2.50±0.6 g, P<sub>D</sub>2 = 5.92±0.05 vs PGF<sub>2α</sub> 10 μM; precontraction = 4.6±0.3 g, P<sub>D</sub>2 = 5.8±0.05, P>0.05). Since both apamin and IbTX (and TEA) induced a similar and modest increase in precontraction levels, their differential effects on NTG-mediated vasorelaxation is not likely to be explained by an effect solely related to changes in precontraction level.

In endothelium-denuded arteries, NTG produced concentration-dependent vasorelaxation (pD<sub>2</sub> = 6.89±0.03; E<sub>max</sub> = 104.0±1.4%) with a 12-fold higher potency than in endothelium intact vessels (Fig. 2A and B). Intriguingly, IbTX did not affect NTG-mediated vasorelaxation in endothelium denuded vessels (Fig. 2B), suggesting an endothelium-dependent interaction between NTG-induced vasodilation and BK<sub>ca</sub>.

Fig. 1. (A) NTG-mediated fall in mean arterial blood pressure (MAP) in conscious rats before (NTG) and during infusion of IbTX (NTG+IbTX). (B) Increase in coronary flow rate in isolated perfused rat hearts. Effect of NTG before (NTG) and after treatment with IbTX (0.1 μM)(NTG+IbTX). (C) Concentration-relaxation curves for NTG in rat coronary arteries preconstricted by PGF<sub>2α</sub>. Arteries were examined after pretreated with IbTX (0.1 μM) or without any pretreatment (control).
than those induced by 80 mM K\(^+\) \((n=15)\). This is a characteristic effect-profile seen with drugs acting by opening of K\(^+\) channels. However, in endothelium-denuded preparations differences in the vasorelaxant effect of NTG elicited by 30 mM K\(^+\) compared with 80 mM K\(^+\) \((n=6)\) was significantly attenuated (Fig. 3A and B). The results suggest, that in endothelium intact vessels, potassium channel opening significantly contributes to NTG-induced vasorelaxation.

5.3.3. Effect of sGC inhibition

The sGC inhibitor NS2028 produced the most prominent blockade of the NTG response (Fig. 2A). Addition of IbTX in the presence of NS2028 did not change the effect of NS2028 (Table 1). In endothelium denuded vessels, NS2028 produced a marked blockade of the NTG response similar to that found in endothelium-intact vessels (Fig. 2B). IbTX did not change the effect of NS2028.

5.3.4. Effect of IbTX on SNP and nimodipine induced vasorelaxation

Like NTG the effect of SNP-derived NO was sig-

![Graph A](image1)

![Graph B](image2)

![Graph C](image3)

![Graph D](image4)

Fig. 3. Concentration-relaxation curves for NTG in isolated porcine coronary arteries preconstricted by 30 mM K\(^+\) or 80 mM K\(^+\). (A) endothelium intact segments. (B) endothelium denuded segments.

Table 1

<table>
<thead>
<tr>
<th>Vasodilator</th>
<th>Pretreatment</th>
<th>(pD_{2,E_{\text{max}}})</th>
<th>(E_{\text{max}}) (%)</th>
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<td>NTG</td>
<td>none</td>
<td>5.80±0.05</td>
<td>97.6±3.2</td>
</tr>
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<td>NTG</td>
<td>IbTX</td>
<td>4.91±0.20*</td>
<td>49.7±6.2*</td>
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<td>NTG</td>
<td>TEA</td>
<td>5.38±0.19*</td>
<td>87.4±11.2</td>
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<td>NTG</td>
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<tr>
<td>NTG</td>
<td>apamin</td>
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<td>NS2028</td>
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<tr>
<td>NTG</td>
<td>IbTX/NS2028</td>
<td>not calculated</td>
<td>13.4±0.9*</td>
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</table>

\(* P<0.05.\)
Fig. 4. Concentration-relaxation curves in isolated porcine coronary arteries preconstricted with PGF$_{2a}$. After pretreatment (20 minutes) with IbTX (0.1 μM), the segments were relaxed by either: (A) sodium nitroprusside (SNP) or (B) nimodipine. Endothelium intact segments.

Fig. 5. Effect of NTG (50 μM) on coronary flow in isolated perfused rat hearts. NTG-mediated changes before (NTG, response=100%) and after infusion of IbTX (0.1 μM, NTG+IbTX) in isolated perfused hearts from normal rats (black bar) and rats pretreated with PEG-SOD (grey bar). PEG-SOD (30000 units/kg) was administered intravenously 16–24 hours before the experiment and added to the perfusion liquid (150 μg/ml).

suggest that IbTX primarily impairs in vivo NTG-mediated vasodilation by preventing NTG-induced opening of BK$_{Ca}$. Further support for this assumption is derived from the myograph experiments showing that NTG (and SNP) preferentially relax contractions induced by 30 mM K$^+$ compared to 80 mM K$^+$. This effect profile, which results from changes in the outward directed electrochemical gradient for K$^+$, is a unique feature of drugs acting by K$^+$ channel opening [12]. A specific interaction between the BK$_{Ca}$ subgroup of potassium channels and NTG-derived NO is suggested by the inhibitory effects on NTG-mediated vasorelaxation induced by TEA and IbTX whereas glibenclamide (which inhibits ATP-sensitive K$^+$ channels) did not modulate NTG-mediated vasorelaxation. IbTX, being the most potent blocker of BK$_{Ca}$, reduced the in vitro vasorelaxant effect of NTG by approximately 50%.

The present in vitro findings are in agreement with limited previous reports showing that in vitro vasorelaxation mediated by nitrovasodilators (SNP, SNAP) and endogenous NO release (acetylcholine) may be influenced by modulation of BK$_{Ca}$ [4]. However, the significance of these findings are further stressed by the present observation, that BK$_{Ca}$ modulation from a quantitative point of view, markedly influences the circulatory response to pharmacological derived NO in isolated perfused hearts and in vivo.

Intriguingly, the proposed BK$_{Ca}$ opening effect of NTG seems to depend upon an intact vascular endothelium. This observation is substantiated by two findings. Firstly, the differential vasorelaxation to 30 mM and 80 mM K$^+$ was significantly diminished after removal of the endothelium.

6. Discussion

The main findings of this study are: 1) that in vivo NTG-mediated hypertensive effects are markedly inhibited by blockade of BK$_{Ca}$; and 2) that this inhibitory effect apparently depends upon an intact vascular endothelium.

In the present study infusion of IbTX reduced the hypertensive effect of NTG by approximately 55%. Because IbTX had no hemodynamic effects per se, the results

Fig. 5. Effect of NTG (50 μM) on coronary flow in isolated perfused rat hearts. NTG-mediated changes before (NTG, response=100%) and after infusion of IbTX (0.1 μM, NTG+IbTX) in isolated perfused hearts from normal rats (black bar) and rats pretreated with PEG-SOD (grey bar). PEG-SOD (30000 units/kg) was administered intravenously 16–24 hours before the experiment and added to the perfusion liquid (150 μg/ml).

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Intriguingly, the proposed BK$_{Ca}$ opening effect of NTG seems to depend upon an intact vascular endothelium. This observation is substantiated by two findings. Firstly, the differential vasorelaxation to 30 mM and 80 mM K$^+$ was significantly diminished after removal of the endothelium.
Secondly, IbTX, in accordance with some previous reports [13], did not affect NTG-mediated vasorelaxation in endothelium denuded vessels. Removal of the endothelium also significantly affected the vascular sensitivity to NTG (leftward shift of the concentration-relaxation curve). Together these observations may suggest, that the endothelium in a BKCa dependent manner, either release a contracting factor and/or may increase the degradation of NO. However, incubation with l-NA, indomethacin or the endothelin receptor antagonist BQ-123 did not affect the response to IbTX. Thus the effect of IbTX at least seems independent of a potential depolarization-induced release of prostaglandins or endothelin from the endothelium or from other counterregulatory vasoconstrictor mechanisms caused by continuous endogenous NO formation. In contrast, scavenging of O2 with PEG–SOD significantly diminished the effect of IbTX in the isolated perfused heart (Fig. 5). Recent data suggest, that superoxide anions produced by the endothelium may inactivate NO before it reaches the vascular smooth muscle guanylate cyclase [14]. Interestingly, hyperpolarizing agents like the potassium channel opening agents pinacidil and hydralazine inhibit vascular superoxide anion formation [15,16], an effect which can be blocked by pretreatment with depolarizing agents. This implies, that the activity of endothelial oxidases, the production of superoxide anions and ultimately the bioavailability of NO may be regulated by the membrane potential. Thus, it is possible that activation and inhibition of endothelial BKCa, may augment and impair NO-mediated vasorelaxation, respectively. The present results are compatible with this assumption.

It has previously been suggested, that NO may activate BKCa directly [17]. The present finding, that guanylate cyclase inhibition with NS2028 completely blocks the vasoactive effect of NO derived from NTG does not support this hypothesis. Instead, our data are in agreement with reports showing an interaction between NO and BKCa through activation of cGMP [4,18].

In conclusion, the results show that the ex vivo and in vivo vascular effects of NTG are significantly impaired by inhibition of BKCa. This interaction appears to be strongly endothelium dependent and may be attenuated by scavenging of superoxide anions. The results suggest, that activation of endothelial BKCa contributes to the vasorelaxant effects of NTG-derived NO partly through inhibition of endothelial O2 production. It is concluded, that endothelial large conductance calcium-activated K+ channels modulates the response to NTG-derived NO. This effect is most likely caused indirectly through membrane potential-mediated changes in superoxide formation and thus the vascular bioavailability of NO.

References


