Effect of Somatostatin on Rabbit Isolated Coronary Arteries

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Received February 22, 2002 Accepted June 18, 2002

ABSTRACT—Somatostatin analogues are capable of inhibiting vascular smooth muscle and endothelial cell proliferation. However, little is known about the effect of somatostatin on vascular responses in endothelium-denuded coronary arteries in vitro. The aim of this work was to determine whether or not somatostatin prevented the contractile response induced by 5-hydroxytryptamine and acetylcholine in endothelium-denuded rabbit coronary arteries. Somatostatin attenuated the contraction produced by 5-hydroxytryptamine in both proximal (PC) and distal coronary (DC) arteries (contraction induced by 10^{-6} M 5-hydroxytryptamine was inhibited by 10^{-6} M somatostatin by 90.8 ± 11.0% (P<0.001, n = 9) and by 46.2 ± 14.0% (P<0.05, n = 9) in DC and PC, respectively), but concentration-dependently decreased the contraction induced by U46619 (11α-epoxy-methanoprostaglandin F_{2α}) only in PC arteries, suggesting that the response of PC and DC arteries to somatostatin were qualitatively different. Furthermore, we suggest that somatostatin may enhance acetylcholine-induced relaxation by combination of increasing endothelium-dependent relaxation (by a NO-dependent mechanism) and blocking contraction at the muscle level.

Keywords: Somatostatin, Coronary artery, Acetylcholine, 5-Hydroxytryptamine, Nitric oxide

Vascular diseases as well as surgical interventions such as coronary angioplasty induce endothelial denudation (1, 2) in coronary arteries. Loss of the endothelial layer alters vascular responses to certain agonists; thus 5-hydroxytryptamine and acetylcholine, which induce vasodilatation in normal coronary arteries, might be impaired or even turn into vasoconstriction in endothelium-denuded coronary arteries, leading to coronary spasm (1, 3, 4). In addition, thromboxane A_2 released by platelets (5) is another candidate for the mediation of coronary vasospasm (6) since it is found in increasing concentration at the site of coronary arterial stenosis (7).

Somatostatin (SRIF) is a neuroendocrine peptide (8) that exerts a wide range of physiological actions. However, the vascular effects of somatostatin are still unclear. A variety of studies have demonstrated species and regional differences in the blood flow responses to somatostatin. Thus, while in the rat superior mesenteric artery, octreotide (a somatostatin analogue) boosts vasoconstriction induced by α-agonists (9), in the vascular bed of cats, somatostatin showed opposite effects (10). On the other hand, we and others have shown that, although somatostatin has no effect on arteries kept under resting tension, it relaxes arteries precontracted with noradrenaline in vitro (11, 12). Despite positive effects of somatostatin found in animal models of coronary restenosis, based on the anti-proliferative effect of this peptide on both vascular smooth muscle (13) and endothelial cells (14, 15), little is known about the effect of somatostatin on vascular responses in endothelium-denuded coronary arteries. The purpose of this work was to determine whether or not somatostatin, in an ‘in vitro’ model, was able to prevent the vascular alterations, hypercontractibility as well as impairment in endothelium-dependent relaxation, that occur in endothelium-denuded rabbit coronary arteries.

MATERIALS AND METHODS

General Procedure

The Universidad Complutense de Madrid (EEC official registration 28079-15ABC) approved all protocols concerning animals. Male New Zealand White rabbits weighing 2.5 – 3.0 kg were obtained from Biocentre S.A. (Barcelona, Spain). The animals were anesthetized with ethyl ether and killed by exsanguination from the common carotid arteries. The proximal (PC) and distal coronary (DC) arteries were rapidly removed and placed in Krebs-Henseleit solution (KHS) of the following composition: 119 mM NaCl, 4.7 mM KCl, 25 mM NaHCO_3, 1.0 mM MgSO_4, 11.1 mM

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Adherent fat and surrounding tissue were cleaned off and the PC arteries (internal diameter of 1 mm) were cut into rings of approximately 2 – 3 mm in width. The rings were then suspended between two stainless steel hooks in organ baths containing 10 ml of KHS. The solution was kept at 36.0 ± 0.5°C and gassed continuously with a 95% O₂ – 5% CO₂ gas mixture. The PC rings were mounted under 0.5-g resting tension. Each preparation was allowed to equilibrate for 60 – 90 min. Contractile responses were measured isometrically by means of force-displacement transducers (Grass FT 03) and were recorded on a Grass polygraph as previously described (16). The isometric force was also digitalized by a MacLab A/D converter (Chart v3.2; AD Instruments Pty. Ltd., Castle Hill, Australia) and stored and displayed on a Mackintosh computer (17).

Using a dissecting microscope, a segment of the distal coronary (DC) artery (approximately 1.5 mm in length, internal diameter of 200 μm), was carefully dissected free of connective tissues. The artery was mounted in a small vessel myograph (Multy Myograph system 610M) containing 2 ml of KHS using 40 μm tungsten wires (California Fine Wire Company, Grover City, CA, USA). The vessel was set to a tension equivalent to that generated at 0.9 times the diameter of the vessel at 100 mmHg transmural pressure (18). Vessels were allowed to equilibrate at 37 ± 0.5°C and gassed continuously with a 95% O₂ – 5% CO₂ gas mixture. The isometric force was also digitalized by Myodaq 2.01 program (Danish Myo Technology, Copenhagen, Denmark) and stored and displayed on a personal computer (17).

The arteries were divided into two groups and the endothelium was removed in one group of arteries (arteries, −E). These were prepared mechanically by inserting a stainless-steel rod into the rings and rubbing the rings gently. In the other group the endothelium was kept intact (arteries, +E). In previous experiments with rabbit coronary arteries, time-control experiments with vehicle were established (data not shown). After equilibration, the following experiments were carried out.

**Experimental procedure**

**Contraction test:** In the first group of experiments, both PC and DC (+E and −E) arteries precontracted with KCl at 30 mM were used to construct a cumulative concentration-response curve for either 5-hydroxytryptamine or acetylcholine by cumulatively adding agonists in 1 log unit increments beginning with 10⁻⁹ M (5-hydroxytryptamine) or 10⁻⁸ M (acetylcholine). After being washed out, the arteries were incubated for 20 min in the presence of somatostatin (10⁻⁶ – 10⁻⁸ M) and the procedure repeated (in previous studies carried out in our laboratory, we found that 20 min was the appropriate time, unpublished data).

In another group of experiments, PC arteries were contracted with 10⁻⁵ M U46619 (an analogue of thromboxane A₂). After washing out the activating agent, the rings were incubated with 10⁻⁸ – 10⁻⁴ M somatostatin for 20 min and the contraction induced by U46619 was repeated.

To address the issue of whether nitric oxide (NO) or a prostanoid is involved in the increase of endothelium-dependent relaxation exerted by somatostatin, experiments were repeated in the presence of a NO synthase inhibitor (l-NAME, 10⁻⁴ M) and a cyclooxygenase inhibitor (indomethacin, 10⁻⁶ M).

**Relaxation test:** To investigate whether somatostatin was able to affect endothelium-dependent and endothelium-independent relaxation in both DC and PC arteries (+E and −E), a precontraction with 30 mM K⁺ was induced, and when a plateau was reached, the following cumulative relaxation curves were made by adding aliquots of the relaxing agonist: A concentration-response curve to acetylcholine (10⁻⁸ – 10⁻⁶ M) and a concentration-response curve to sodium nitroprusside (10⁻⁶ – 10⁻⁴ M). After being washing out the agonist, the arteries were incubated for 20 min in the presence of somatostatin (10⁻⁶ – 10⁻⁴ M) and the concentration-response curve to acetylcholine (10⁻⁸ – 10⁻⁶ M) or to sodium nitroprusside (10⁻⁸ – 10⁻⁴ M) was determined again.

**Drugs**

The following drugs were used: somatostatin, was a generous gift from Serono Laboratories (Madrid, Spain); potassium chloride (Merck, Darmstadt, Germany); 5-hydroxytryptamine creatine sulphate, acetylcholine chloride, sodium nitroprusside, 9,11-dideoxy-9α,N-nitro-L-arginine methyl ester (l-NAME), indomethacin and 11α-epoxy-methanoprostaglandin F₂α (U46619) (Sigma, St. Louis, MO, USA). Stock solutions of all drugs, except U46619, were prepared in deionized water. Stock solutions of U46619 (10⁻² M) were made in 97% ethanol. Working solutions of all drugs were made in KHS. Control experiments had demonstrated that the highest ethanol level used had no effect on the contractile response. The concentration of each chemical or drug is expressed as the final concentration in the bath in terms of the salt. All values used in the analysis represent means ± S.E.M. of seven to nine rabbits in each group. Concentration-response curves were used to determine the concentration of somatostatin, producing 50% inhibition of the maximal contractile response (IC₅₀), using linear regression analysis over the response range of 20 – 80% of the maximal inhibition. Comparisons between the different groups were performed by a two-way ANOVA test. A level of probability of P<0.05 was accepted as statistically significant.
RESULTS

Effect of somatostatin on the concentration-response curves to 5-hydroxytryptamine in endothelium-denuded coronary arteries

We first studied the effect of somatostatin on concentration-response curves to 5-hydroxytryptamine in both distal and PC arteries without endothelium (arteries -E). In DC arteries, somatostatin (10^6 – 10^-4 M) shifted the concentration-response curve induced by 5-hydroxytryptamine (10^-9 – 10^-4 M) downwards and to the right. The maximal contraction induced by 10^-4 M 5-hydroxytryptamine was inhibited by 10^-6 M somatostatin by 90.8 ± 11.0% (P<0.001, n = 9), by 107.2 ± 20.2% (P<0.001, n = 9) with somatostatin 10^-5 M and by 113.1 ± 8.4% (P<0.001, n = 9) with somatostatin 10^-4 M (Fig. 1, left panel).

In addition, in the PC arteries we found similar, but lesser, effects of somatostatin on concentration-responses to 5-hydroxytryptamine. The maximal contraction induced by 10^-4 M 5-hydroxytryptamine was inhibited by somatostatin by 46.2 ± 14.0% (P<0.05, n = 9), by 69.2 ± 11.8% (P<0.001, n = 9) and 84.1 ± 6.4 (P<0.001, n = 7) with 10^-6, 10^-5 and 10^-4 M respectively (Fig. 1, right panel).

Effect of somatostatin on contraction responses induced by U46619 in PC arteries

In another group of experiments, we also investigated the effect of somatostatin at 10^6 – 10^-4 M on contractile responses induced by 10^-5 M U46619 in PC arteries +E. Somatostatin decreased the contraction induced by 10^-5 M U46619 reaching significant values (P<0.05) at concentrations equal to or higher than 10^-6 M. As shown in Fig. 2, the maximal inhibitory effect of 10^-4 M somatostatin was 93.7 ± 9.3% (P<0.001, n = 9).

Effect of somatostatin on the concentration-response curves to acetylcholine in endothelium-denuded coronary arteries

When the endothelium was removed, the relaxation induced by acetylcholine changed to contraction. Acetylcholine caused a contraction in a concentration-dependent manner, as shown in Fig. 3 (left and right panels).

In DC arteries, somatostatin (10^6 – 10^-4 M) shifted the concentration-response curves to acetylcholine downwards and to the right (Fig. 3, left panel). The maximal effect in-
duced by $10^{-6}$ M acetylcholine was $-2.0 \pm 1.0\%$ ($P<0.001$, $n=9$, negative values mean relaxation) in arteries incubated with $10^{-6}$ M somatostatin; $9.3 \pm 15.2\%$ in arteries incubated with $10^{-5}$ M somatostatin and $-5.2 \pm 4.0\%$ in arteries incubated with $10^{-4}$ M somatostatin.

In PC arteries, $10^{-6}$ M somatostatin decreased the sensitivity of these arteries to acetylcholine ($IC_{50} = 2.1 \pm 1.3 \times 10^{-7}$ M in control and $4.9 \pm 1.1 \times 10^{-7}$ M in the presence of $10^{-5}$ M somatostatin), whereas the maximal contractile effect induced by $10^{-6}$ M acetylcholine in arteries $-$E was not modified when these arteries were incubated with somatostatin ($10^{-6} - 10^{-4}$ M) as shown in Fig. 3 (right panel).

**Effect of somatostatin on endothelium-dependent relaxation**

We tested the effect of somatostatin on the endothelium-dependent relaxation induced by acetylcholine ($10^{-8} - 10^{-6}$ M) in both PC and DC arteries. KCl (30 mM) precontracted the vessels to a steady level of force. With this preconstriction, $10^{-8} - 10^{-6}$ M acetylcholine caused a concentration-dependent relaxation in DC arteries with intact endothelium. The maximal relaxation was $45.2 \pm 4.1\%$. Somatostatin at $10^{-5}$ M increased the endothelium-dependent relaxation in these arteries; thus, the maximal effect induced by $10^{-6}$ M acetylcholine in somatostatin-treated arteries was $67.1 \pm 2.0\%$ ($P<0.05$, $n=8$). (Fig. 4, left panel).

![Fig. 3. Effect of somatostatin ($10^{-6} - 10^{-4}$ M) on the concentration-response curves to acetylcholine ($10^{-8} - 10^{-6}$ M) in distal (left panel) and proximal (right panel) endothelium-denuded coronary arteries (E). Endothelium was denuded from coronary arteries mechanically by inserting a rod into the rings and rubbing gently. Somatostatin was incubated for 20 min prior to challenging the arteries with cumulative concentrations of acetylcholine (see Materials and Methods). Each point represents the mean of 9 experiments, and vertical lines indicate S.E.M.](image)

![Fig. 4. Effect of somatostatin ($10^{-5}$ M) on endothelium-dependent relaxation induced by acetylcholine ($10^{-8} - 10^{-6}$ M) in distal (left panel) and proximal (right panel) coronary arteries. Arteries were precontracted with 30 mM KCl in order to reach a stable plateau, and then cumulative concentrations of acetylcholine were added in the absence or presence of somatostatin. Each point represents the mean of 8 experiments, and vertical lines indicate S.E.M. *$P<0.05$ with respect to the control (not incubated with somatostatin).](image)
In PC arteries, acetylcholine ($10^{-8} - 10^{-6}$ M) also induced endothelium-dependent relaxation (arteries +E) in a concentration-dependent manner. The maximal relaxant effect was reached with $10^{-6}$ M acetylcholine (39.0 ± 12.0%). Somatostatin at $10^{-5}$ M did not significantly affect this maximal effect (37.0 ± 10.0% in somatostatin-treated arteries) (Fig. 4, right panel). To address the issue of whether NO or a prostanoid is involved in the potentiation of endothelium-dependent relaxations exerted by somatostatin, experiments were repeated in the presence of a NO synthase inhibitor (L-NAME, $10^{-4}$ M) and a cyclooxygenase inhibitor (indomethacin, $10^{-6}$ M). L-NAME completely abolished the effect of somatostatin on endothelium-dependent relaxation in small DC arteries, whereas indomethacin did not show any effect (Fig. 5, left and right panels).

**Effect of somatostatin on endothelium-independent relaxation**

The effects of somatostatin on endothelium-independent relaxation induced by sodium nitroprusside ($10^{-8} - 10^{-4}$ M) were also studied in both groups of coronary arteries (distal and proximal arteries +E). Sodium nitroprusside induced a relaxant effect in a concentration-dependent manner in both groups of arteries previously contracted with 30 mM KCl.

![Fig. 5](image1.png)

**Fig. 5.** Effects of NO synthesis inhibition by L-NAME (left panel) and indomethacin (right panel) on the increasing effect of somatostatin on endothelium-dependent relaxation in small distal coronary arteries. Arteries were precontracted with 30 mM KCl in order to reach a stable plateau and then, cumulative concentrations of acetylcholine were added in the absence or presence of somatostatin. Arteries were incubated with L-NAME ($10^{-4}$ M) or indomethacin ($10^{-6}$ M) for 30 min and the same procedure was repeated. Each point represents the mean of 9 experiments, and vertical lines indicate S.E.M. **P<0.01, ***P<0.001 with respect to control (not incubated with somatostatin).

![Fig. 6](image2.png)

**Fig. 6.** Effect of somatostatin ($10^{-6} - 10^{-4}$ M) on endothelium-independent relaxation induced by sodium nitroprusside (SNP) in distal (left panel) and proximal (right panel) coronary arteries. Arteries were precontracted with 30 mM KCl in order to reach stable plateau and then, cumulative concentrations of sodium nitroprusside were added in the absence or presence of somatostatin. Each point represents the mean of 7 experiments, and vertical lines indicate S.E.M.
K⁺, the maximal relaxation being 87.1 ± 4.0% and 83.0 ± 6.0%, with respect to the control (100%) in DC and PC arteries, respectively. We did not find any effects on the endothelium-independent relaxation in DC and PC arteries when these were incubated in the presence of somatostatin at 10⁻⁶ – 10⁻⁴ M. Thus, the maximum relaxant effect induced by 10⁻⁴ M sodium nitroprusside was 71.9 ± 8.0%, 71.8 ± 12.0%, 71.9 ± 14.0% in DC arteries and 72.9 ± 14.0%, 72.8 ± 9.2%, 51.9 ± 28.4% in PC arteries (Fig. 6, left and right panels).

**DISCUSSION**

In the present in vitro study, the effect of somatostatin on vascular responses in both rabbit coronary arteries with intact endothelium and with mechanically denuded endothelium has been investigated. Endothelium-denuded coronary arteries have been chosen as an in vitro model of endothelium-damaged coronary artery produced by angioplasty.

Both DC and PC arteries studied exhibited contractile responses to 5-HT when the endothelium was denuded. Somatostatin (10⁻⁶ – 10⁻⁴ M) shifted the concentration-response curve to 5-HT downward and to the right in both arteries, but it proved to be more potent in DC arteries than in PC arteries (in DC arteries, somatostatin turned the responses induced by 5-HT from vasoconstriction to vasodilatation). Contractile synergism between 5-hydroxytryptamine and other vasoconstrictor substances has been observed in a number of peripheral and cerebrovascular blood vessels (19). In some animal coronary artery models (20, 21), as well as in human coronary arteries (22, 23), a contractile synergistic effect between 5-hydroxytryptamine and U46619 has been demonstrated.

Somatostatin was also shown to decrease contractions induced by cumulative concentration of acetylcholine in endothelium-denuded small coronary arteries and yet again showed no effect on large PC arteries.

In addition, we tested the effect of somatostatin on the contraction induced by U46619 (an analogue of thromboxane A₂) in PC arteries. Somatostatin decreased the contractile responses induced by U46619 in a concentration-dependent manner.

We also found that somatostatin boosted the endothelium-dependent relaxation induced by acetylcholine in small DC arteries (but not in large PC arteries) and that this effect was blocked by preincubating the arteries with the NO synthase inhibitor L-NAME, suggesting a NO-mediated mechanism. The coronary vascular response to acetylcholine is predominantly due to an increased production of NO. Parent et al. (24) demonstrated that L-NAME inhibited the endothelium-dependent relaxation induced by acetylcholine only in distal coronary arteries, but not in proximal coronary arteries, which is evidence for the significance of endothelium-dependent relaxation due to NO in distal coronary arteries. In addition, NO release has been implicated in the control of distal coronary blood flow but not of that in the proximal coronary artery (25). Our results here agree with previous studies that showed an enhancing effect of endothelium-dependent relaxation in rabbit aorta arteries by angiopeptin (a somatostatin analogue) (26). It has also been shown that somatostatin-induced vasodilatation in noradrenaline-precontracted arteries is mediated by NO since it is blocked by L-NAME (10, 27, 11).

In general, somatostatin has been shown to be more effective in small coronary arteries than in large coronary arteries throughout this work. These findings are in agreement with those by Dezsi et al. (10) who found that somatostatin has a vasodilator effect on noradrenaline-precontracted small mesenteric arteries but none on large mesenteric arteries, and also with our previous paper in which we reported that somatostatin was a more potent vasodilator of rabbit small mesenteric arteries than of aorta arteries (12). The concentrations of somatostatin used in this study are apparently high. However, therapeutic doses of somatostatin (up to 250 μg) applied in clinical and experimental studies may result in high (10⁻⁴ M) plasma concentrations, activating indirect or less sensitive direct vasoconstrictive pathways.

Although not the aim of this study, it is interesting to note that the effects of somatostatin described may be mediated by one or more of the 5 somatostatin receptors described, SSTR-1 through -5 (28, 29), that can be divided into two subgroups through sequence similarity and affinity for somatostatin analogs (28). The first subgroup of receptors, including SSTR-2, -3 and -5, has a high affinity for somatostatin-14, somatostatin-28 and somatostatin analogues such as angiopeptin. The second subgroup, including SSTR-1 and -4, has a high affinity for somatostatin-14, but a lower affinity for the majority of the somatostatin analogues. The pattern of SSTR subtype expression in atherosclerotic vessels did not differ significantly from that found in normal vascular tissue. SSTR-1, but not SSTR-2, was predominantly expressed on the surface of endothelial cells (30). The localization of SSTR-1 in endothelial cells is consistent with the finding that removal of endothelial cells abolished the vascular effect of somatostatin (31, 32). All five receptors are coupled to G-proteins and affect a number of distinct signal transduction pathways (33, 34). All five receptors are also functionally coupled to inhibition of adenyl cyclase (35). Some of the receptors isotypes also modulate other effects such as phosphotyrosine phosphatase, K⁺ and voltage-dependent Ca²⁺ ion channels, a Na⁺/H⁺ exchanger, phospholipase C, phospholipase A₂ and mitogen-activated protein kinase (MAPK) (35). SSTR1-4 acts by stimulating PTP, which dephosphorylates receptor
tyrosine kinase, thereby attenuating the mitogenic signal (35). SSTR-5, on the other hand, inhibits guanylate cyclase, cGMP-dependent phosphorylation and activation of MAPK (35). More experiments with selective agonists and antagonists are required to determine in detail the receptors involved and the mechanism of action by which somatostatin acts.

In conclusion, somatostatin pretreatment decreased vasoconstriction induced by 5-hydroxytryptamine, U46619 or acetylcholine in coronary arteries and increased endothelium-dependent relaxation in DC arteries, without affecting endothelium-independent relaxation.

Acknowledgment

This work was supported in part by a FISS grant (99/0930).

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