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Endogenous prostacyclin increases neuronal nitric oxide release in mesenteric artery from spontaneously hypertensive rats

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Abstract

The aim of this study was to analyse the possible influence of endogenous prostacyclin on neuronal nitric oxide (NO) release induced by electrical field stimulation in mesenteric arteries from spontaneously hypertensive rats (SHR). Preincubation with the prostacyclin synthesis inhibitor tranylcypromine decreased NO release induced by electrical field stimulation, which was reversed by exogenous prostacyclin. Preincubation with tranylcypromine increased basal and electrical field stimulation-induced [^{3}H]noradrenaline release. The nitric oxide synthase inhibitor N^{ω}-nitro-L-arginine methyl esther (L-NAME) increased the vasoconstrictor response induced by electrical field stimulation. In the presence of tranylcypromine, L-NAME did not modify the vasoconstrictor response induced by electrical field stimulation. In the presence of tranylcypromine and prostacyclin, L-NAME increased the vasoconstrictor response to electrical field stimulation. These results indicate that endogenous prostacyclin positively modulates the neuronal NO release induced by electrical field stimulation and that this neuronal NO participates in the regulation of the vasomotor response.

Keywords: Prostacyclin; Nitrergic innervation; Mesenteric artery

1. Introduction

Vascular tone is determined by an equilibrium among several mechanisms, in which innervation plays an important role. This regulation involves the adrenergic, cholinergic, nitrergic, peptidergic and/or sensory innervation that are specific to the vascular bed considered. Nitric oxide (NO) is an important neurotransmitter in both the peripheral (Marín and Balfagón, 1998) and central nervous (Bredt et al., 1992) systems. Perivascular nitrergic innervation has been described in several vascular beds, including the cerebral (Estrada et al., 1993) and mesenteric arteries (Marín and Balfagón, 1998).

Prostanoids play many important roles in a variety of physiological and pathophysiological processes in the body, including hypertension (Zhao and Richardson, 1990). Prostacyclin is an endogenous prostanoid that is produced in all body tissues, including vascular wall (Vane and Corin, 2003). Prostacyclin is the major prostanoid synthesized by rat mesenteric arteries (Desjardins-Giasson et al., 1982), and its release is decreased (Jaiswal et al., 1993; Matrougui et al., 1997; Szekacs et al., 1997), unchanged (Desjardins-Giasson et al., 1984; Lennon and Poyser, 1986) or increased (McGowan and Vandongen, 1989, Zhao and Richardson, 1990; Blumberg et al., 2002) in hypertension. An interaction between the prostacyclin and nitric oxide synthase (NOS) pathways has been reported (Shimokawa et al., 1988; Zellers et al., 2000; Pérez-Sala and Lamas, 2001). We have reported that electrical field stimulation induces neuronal NO release in mesenteric arteries from spontaneously hypertensive rats (SHR), but that arteries from normotensive rats did not release neuronal NO (Marín et al., 2000). However, neuronal NO release can be induced in mesenteric arteries from normotensive rats in the presence of prosta-

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cyclin through a mechanism involving cAMP-protein kinase A (PKA) activation (Ferrer et al., 2004).

With this in mind, it is reasonable to hypothesize that endogenous prostacyclin could modulate neuronal NO release in hypertension. Therefore, the aim of this work was to study the possible role of endogenous prostacyclin in neuronal NO release and the involvement of the latter in the vasomotor response in rat mesenteric artery from SHR rats.

2. Materials and methods

2.1. Tissue preparation

Male 6-month-old SHR rats (250–300 g) were used. They were sacrificed by CO_2 inhalation. The investigation conforms to the Guide for the Care and Use of Laboratory Animals published by the U.S. National Institutes of Health (NIH publication No. 85.23, revised 1996). The first branch of the mesenteric artery was carefully dissected out, cleaned of connective tissue and placed in Krebs–Henseleit solution (KHS) at 4 °C. In the present work, we used endothelium denuded segments to eliminate this source of vascular NO and avoid the possible actions by different study drugs on the endothelial cells, which could lead to the misinterpretation of results. The absence of vascular endothelium was tested by the inability of acetylcholine to relax segments precontracted with noradrenaline.

2.2. Nitric oxide release

The electrical field stimulation induced NO release was estimated as nitrites in the medium. Denuded rat mesenteric artery segments (26.4±3.2 mg) were immersed for 30 min in 10 ml of KHS at 37 °C, continuously gassed with a 95% O_2–5% CO_2 mixture (stabilization period). Afterwards, the arteries were transferred to a 500-μl chamber containing two parallel platinum electrodes, 0.5 cm apart, connected to a stimulator (Grass, model S44), for electrical field stimulation. After two washout periods of 6.5 min, the medium was collected to measure the basal release of NO. Once the chambers had been refilled, cumulative electrical field stimulation periods of 30 s at 1, 2, 4 and 8 Hz at 1-min intervals were applied, and then the medium was taken from the bath to measure the concentration of nitrites, according to the colorimetric method based on the Griess reaction (Griess, 1979). To eliminate the possibility that electrical field stimulation induced nitrite production in the incubation medium, experiments were also performed in the absence of tissue.

Experiments were performed in the presence of the neuronal toxin tetrodotoxin (0.1 μM) to confirm the neuronal origin of the NO. The arteries were incubated with the synthesis prostacyclin inhibitor tranylcypromine to study the effect of the endogenous prostacyclin in NO release. The drug was added 30 min before the electrical field stimulation. In another set of experiments, segments were preincubated with tranylcypromine plus prostacyclin.

The stimulation-induced NO release was calculated by subtracting the basal NO release from the electrical field stimulation evoked release. The amount of NO released was expressed in pmol/mg tissue.

2.3. Tritium release

Segments of rat mesenteric arteries of 4 mm in length were set up in a nylon net and immersed for 30 min in 10 ml of KHS at 37 °C, continuously gassed with a 95% O_2–5% CO_2 mixture (stabilization period). Thereafter, they were incubated for 60 min in 1 ml bubbled KHS at 37 °C containing (±)-[^{3}H]noradrenaline (0.33 μM, 10 μCi/ml, sp. act. 10 Ci/mmol). Afterwards, the arteries were transferred to a superfusion chamber with two parallel platinum electrodes, 0.5 cm apart, connected to a stimulator (Grass, model S44) for electrical field stimulation. The arteries were superfused at a rate of 2 ml/min with oxygenated KHS at 37 °C for 100 min, during which time the steady-state level of basal tritium efflux was reached. Then, two electrical stimulation periods of 60 s (200 mA, 0.3 ms, 4 Hz; S1 and S2) were applied to the arteries at 60-min intervals, and the superfusate was collected in vials (10 in total) at 30-s intervals. These vials were collected in the following manner: two before stimulation, to determine the basal level of tritium efflux, two during and six after the stimulation; the latter were enough to recover the basal level of tritium efflux. Afterwards, Ready-Protein solution (Beckman) was added to the vials, and radioactivity was measured in a scintillation counter (Beckman LS 5000 TD). To interfere with tritium release, tranylcypromine (10 μM) was administered 30 min before S2.

The stimulation-induced tritium release was calculated by subtracting the basal tritium release (b1 and b2) from that evoked by electrical stimulation (S1 and S2). Thereafter, the ratio of the net tritium release between S1 and S2 was calculated to eliminate differences between the arteries. The action of the drug on the evoked release was expressed as its effect on this ratio. The amount of radioactivity released was expressed in dpm/mg.

2.4. Vascular reactivity

The method used for isometric tension recording was described by Nielsen and Owman (1971) and modified by Marín and Balfagón (1998). Briefly, two parallel stainless-steel pins were introduced through the lumen of the vascular segment: one fixed to the bath wall and the other connected to a force transducer, and this was connected, in turn, to a polygraph. For electrical field stimulation experiments, segments were mounted between two plati-

num electrodes 0.5 cm apart, connected to a stimulator (Grass, model S44), modified to supply the adequate current strength. Segments were suspended in an organ bath containing 5 ml of KHS solution at 37 °C, continuously bubbled with a 95% O_2–5%CO_2 mixture (pH 7.4). The segments were subjected to a tension of 0.5 g that was readjusted every 15 min during a 90-min equilibration period before drug administration. After this, the vessels were exposed to 75 mM K^+ to check their functional integrity. Endothelium removal did not alter the contractions elicited by 75 mM K^+. After a washout period, the absence of vascular endothelium was proven by the inability of 10 μM acetylcholine to relax segments precontracted with 0.1 μM noradrenaline.

Frequency-response curves to electrical field stimulation (1, 2, 4 and 8 Hz) were performed. The parameters used for the electrical field stimulation were 200 mA and 0.3 ms for 30 s, with an interval of 1 min between each stimulus, the time required to recover basal tone. A washout period of at least 1 h was necessary to avoid desensitisation between consecutive curves. Three successive frequency-response curves, separated by 1-h intervals, produced similar contractile responses.

To analyse the possible role of endogenous prostacyclin in neuronal NO release induced by electrical field stimulation, 10 μM tranylcypromine was added to the bath 30 min before the second electrical field stimulation curve and 100 μM L-NAME plus tranylcypromine before a third curve. Another set of experiments was performed to confirm that endogenous prostacyclin increases neuronal NO release; tranylcypromine plus prostacyclin were added before the first curve and tranylcypromine plus prostacyclin plus L-NAME before the second curve.

In another set of experiments, we analysed the effect of exogenous prostacyclin (50 nM) on neuronal NO release induced by electrical field stimulation. Prostacyclin was added to the bath 30 min before the second frequency-response curve and prostacyclin plus L-NAME, before a third curve, to study this possible effect.

To determine the possible effect of prostacyclin, tranylcypromine or L-NAME on the noradrenaline-induced vasoconstrictor response, these drugs were added to the bath 30 min before performing the noradrenaline concentration-response curve.

2.5. Solutions and drugs

The composition of KHS was as follows (mM): NaCl 115, $CaCl_2$ 2.5, KCl 4.6, KH_2PO_4 1.2, $MgSO_4 7H_2O$ 1.2, $NaHCO_3$ 25, glucose 11.1 and Na_2 EDTA 0.03 (to prevent the oxidation of unstable substances). The drugs used were tranylcipromine, L-NAME hydrochloride, prostacyclin sodium salt, L-noradrenaline hydrochloride, acetylcholine chloride and tetrodotoxin (Sigma, St. Louis, MO, USA). (±)-[^{3}H]noradrenaline hydrochloride was from New England Nuclear (Boston, MA, USA). The stock solutions (10 mM) of the drugs were made in distilled water, except for noradrenaline, which was dissolved in an NaCl (0.9%)–ascorbic acid (0.01% w/v) solution. The solutions were kept at −20 °C, and appropriate dilutions were made in KHS on the day of the experiments.

2.6. Statistical analysis

The responses elicited by electrical field stimulation or by noradrenaline were expressed as a percentage of the contraction induced by 75 mM K^+ to examine the effect of the drugs within each group. Results are given as means±S.E.M. Statistical analysis was done by comparing the curve obtained in the presence of the different substances with the previous or control curve by means of repeated-measure analysis of variance (ANOVA), followed by the Bonferroni test. A p value of less than 0.05 was considered significant. A Student's t-test for unpaired experiments was used.

3. Results

3.1. Nitrites release experiments

Basal nitrites formation was not detected in the medium in either the absence or presence of tranylcypromine or tranylcypromine plus prostacyclin. Electrical field stimulation induced nitrites formation, which was strongly decreased by tetrodotoxin and the prostacyclin synthesis inhibitor tranylcypromine ($p<0.05$, Table 1). The inhibitory effect of tranylcypromine was reversed by the addition of exogenous prostacyclin ($p<0.05$, Table 1).

3.2. Tritium release experiments

Electrical stimulation induced tritium release; the release obtained in S2 was similar to that found in S1 (S1=1580±110, S2=1430±123 dpm/mg; n=5, $p>0.05$). Preincubation with tranylcypromine before S2 increased the S2/S1 ratio (Fig. 1A). Basal tritium release (b1=157±17 and b2=135±15 dpm/mg) was also increased by tranylcypromine (Fig. 1B).

Table 1
Effect of tetrodotoxin, tranylcypromine or tranylcypromine plus prostacyclin (50 nM) on nitrites release induced by electrical field stimulation in mesenteric arteries from SHR rats

	(pmol/mg)
Control	11±0.06
0.1 μM tetrodotoxin	undetected*
10 μM tranylcypromine	2.8±0.08*
10 μM tranylcypromine+50 nM prostacyclin	14.5±0.01#

Results (mean±S.E.M.) are expressed in pmol/mg tissue. n=5–7.
* $p<0.05$ vs. control.
# $p<0.05$ vs. tranylcypromine.

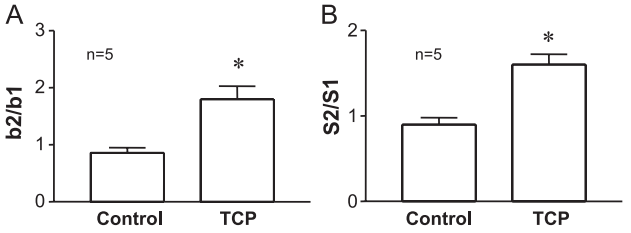

Fig. 1. Tritium release in basal conditions (A) and after electrical field stimulation (B) in the absence or presence of tranylcypromine (TCP). Results (means±S.E.M.) are expressed as the ratios b2/b1 for basal conditions or S2/S1 for electrical field stimulated mesenteric arteries. *n*, number of animals; **p*<0.05 vs. tritium release in absence of TCP.

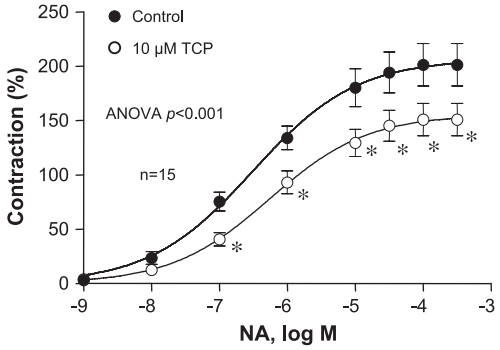

Fig. 3. Effect of tranylcypromine (TCP) on the noradrenaline-response curve performed in mesenteric artery segments from SHR rats. Results (means±S.E.M.) are expressed as a percentage of a previous tone with 75 mM K^+ (895±74 mg). *n*, number of animals. **p*<0.05 vs. control.

3.3. Vascular reactivity

The NOS inhibitor, L-NAME, increased the vasoconstrictor response induced by electrical field stimulation in endothelium-denuded segments (Fig. 2). Prostacyclin (50 nM; *n*=7) alone did not modify the response to electrical field stimulation or the effect of L-NAME (data not shown). The incubation of segments with 10 μM tranylcypromine induced a sustained increase in tension, which stabilised at 584±58 mg, and this effect was abolished by the presence of phentolamine (1 μM). In addition, tranylcypromine increased the contractile response induced by electrical field stimulation and abolished the effect of L-NAME (Fig. 2). In segments pretreated with tranylcypromine plus prostacyclin, L-NAME recovered its ability to enhance the vasoconstrictor response to electrical field stimulation (Fig. 2). When the increase of basal tone induced by tranylcypromine was mechanically eliminated, the effects of tranylcypromine, tranylcypromine plus prostacyclin and of tranylcypromine plus prostacyclin plus L-NAME were similar to their effect on the tensed segments.

The contraction induced by exogenous noradrenaline (1 nM–10 μM) was decreased by the treatment with tranylcypromine (Fig. 3) and remained unmodified by prostacyclin (50 nM; *n*=7) (results not shown). The treatment with tranylcypromine decreased the E_{max} (control=201.3±19.5; tranylcypromine=150.9±14.8; $p<0.05$) and did not modify the pEC_{50} values (control=6.56±0.11; tranylcypromine=6.26± 0.09; $p>0.05$).

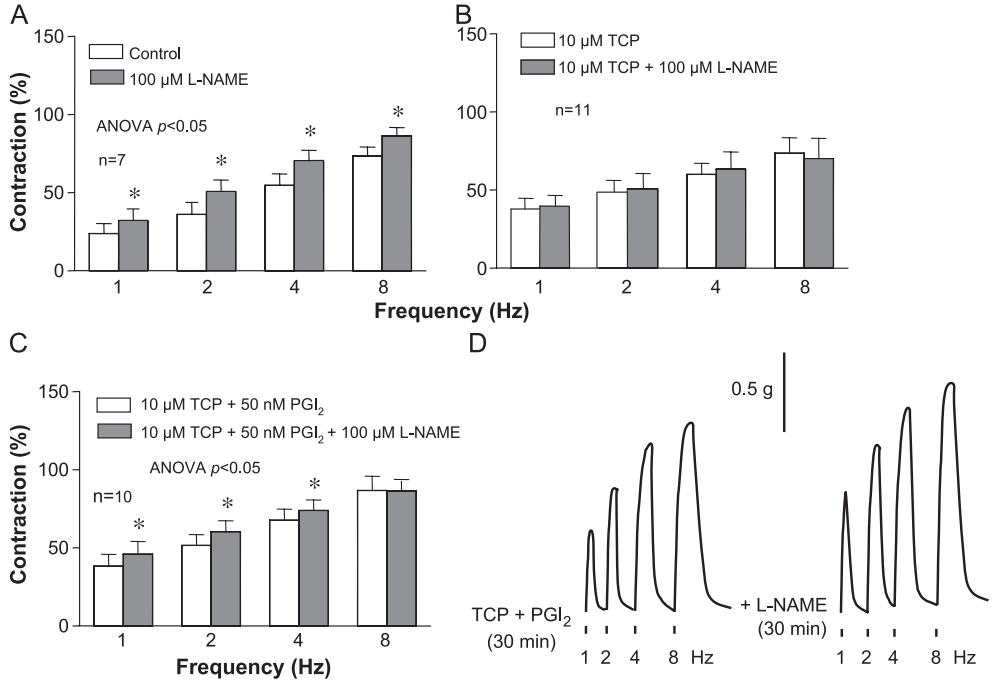

Fig. 2. Effect of L-NAME on the frequency-response curve performed in mesenteric artery segments from (A) SHR rats, (B) with tranylcypromine (TCP) and (C) with TCP plus prostacyclin (PGI_2); (D) A representative registry from Panel C. Results (means±S.E.M.) are expressed as a percentage of a previous tone with 75 mM K^+ (923±120 mg). *n*, number of animals; **p*<0.05 vs. the absence of L-NAME.

4. Discussion

Our results show that endogenous prostacyclin increases the neuronal NO release induced by electrical field stimulation in mesenteric arteries from SHR rats, and that this release participates in the vasomotor response.

In previous works, we reported the functional role of the neuronal NO released by electrical field stimulation in mesenteric arteries from SHR rats (Marín et al., 2000), which have recently quantified (Ferrer et al., 2003), while arteries from normotensive rats do not show this release (Ferrer et al., 2004). We also found that electrical field stimulation can induce NO release by mesenteric arteries from normotensive rats in the presence of prostacyclin (Ferrer et al., 2004). On the other hand, prostacyclin release from the vascular wall, including rat mesenteric artery, is decreased (Jaiswal et al., 1993; Matrougui et al., 1997; Szekacs et al., 1997), unchanged (Desjardins-Giasson et al., 1984; Lennon and Poyser, 1986) or increased (McGowan and Vandongen, 1989, Zhao and Richardson, 1990; Blumberg et al., 2002) in hypertension. Taking into account these results, here, we analyse the possibility that prostacyclin could modulate the NO release induced by electrical field stimulation in mesenteric arteries from SHR rats. The fact that tetrodotoxin significantly decreased the nitrite release induced by electrical field stimulation indicates that the NO came from nerve endings and rules out other possible origins, such as smooth muscle cells (Cernadas et al., 1998; Yan et al., 1999) or adventitia (Zhang et al., 1999), since this basal NO release is not abolished by tetrodotoxin (Ferrer et al., 2003). Therefore, we studied the effect of the prostacyclin synthesis inhibitor tranylcypromine on the neuronal NO release and vasomotor response induced by electrical field stimulation. The amount of nitrites released was significantly diminished by tranylcypromine, and this decrease was reversed by the addition of exogenous prostacyclin. These findings suggest that, in mesenteric arteries from SHR rats, endogenous prostacyclin modulates NO release in a way that is similar to the effect of exogenous prostacyclin on segments from normotensive rats (Ferrer et al., 2004).

Since nitrergic innervation participates in the modulation of the vasomotor response (Marín and Balfagón, 1998), the above results suggest that prostacyclin could participate in the regulation of the vasomotor response induced by electrical field stimulation through a mechanism involving neuronal NO release. The presence of tranylcypromine increased basal tone and vasoconstrictor responses induced by electrical field stimulation. These results could be explained by the decrease in neuronal NO release induced by tranylcypromine. However, the facts that tranylcypromine increased [^{3}H]-noradrenaline release and that phentolamine abolished the increase in basal tone induced by tranylcypromine indicate that the tranylcypromine induced an increase of noradrenaline within the synaptic cleft, probably through its ability to decrease the neurotransmitter metabolism. On the other hand, tranylcypromine has been reported to increase, as well as to decrease, the adrenergic-receptor-mediated response (Grana et al., 1991; Xiang and McNeill, 1992). In our experimental conditions, tranylcypromine reduced the response to noradrenaline, and this effect was more marked at high than at low noradrenaline doses. These results indicate that the increased vasoconstrictor response induced by electrical field stimulation in the presence of tranylcypromine involves other mechanism, in addition to the decreased neuronal NO release, increased noradrenaline release and decreased vasoconstrictor response to noradrenaline observed in these experiments. L-NAME potentiated the electrical field stimulation induced vasoconstriction in our deendothelised preparations, as previously reported (Marín et al., 2000), indicating participation by neuronal NO release in electrical field stimulation responses. To assess if the decrease in neuronal NO release induced by tranylcypromine affected vasomotor responses, we evaluated the effect of this drug on the potentiator effect induced by L-NAME. Tranylcypromine abolished this effect, and the L-NAME potentiator effect was recovered when segments were incubated with tranylcypromine plus exogenous prostacyclin. These results suggest that an endogenous release of prostacyclin could participate in vasomotor responses through the increased neuronal NO release. It is important to note that, although prostacyclin increased the neuronal NO release, it did not modify the vasoconstrictor response to electrical field stimulation in segments pretreated with tranylcypromine. This may be because the amount of exogenous prostacyclin could modify factors other than neuronal NO, and these factors could participate in the vasomotor response to electrical field stimulation (Hoang et al., 2003).

A neuronal release has been described as the origin of the endogenous prostacyclin (Sherbourne et al., 1992), but to our knowledge, neuronal prostacyclin release has not been described in this artery. In addition, we observed that, in our experimental conditions, prostacyclin needed long exposure to have any effect, and this observation argues against the prostacyclin having a neuronal origin, although it does not discard the possibility of prostacyclin release from smooth muscle cells (Frias et al., 2003) and/or fibroblast (Gallagher et al., 1998).

In addition, the response to electrical field stimulation in the absence and in the presence of L-NAME was not affected by exogenous prostacyclin. This indicates that endogenous prostacyclin would have a maximal effect on neuronal NO release. We consider these results to be important since they indicate that exogenous prostacyclin modulates neuronal NO release in normotension (Ferrer et al., 2004), while endogenous prostacyclin also modulates neuronal NO release and thereby counteract the increased vascular resistance in hypertension.

In conclusion, our results demonstrate that endogenous prostacyclin positively modulates neuronal NO release in

mesenteric arteries from hypertensive rats and that this neuronal NO participates in the regulation of the vasomotor response to electrical field stimulation.

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