L-NAME enhances responses to atrial natriuretic peptide in the pulmonary vascular bed of the cat

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Hyman, Albert L., Bracken J. De Witt, Bulent Gumusel, Quingzhong Hao, Philip J. Kadowitz, and Howard L. Lippton. L-NAME enhances responses to atrial natriuretic peptide in the pulmonary vascular bed of the cat. J Appl Physiol 90: 2101–2108, 2001.—This study investigated the hypothesis that atrial natriuretic peptide (ANP) responses are mediated by particulate guanylate cyclase in the pulmonary vascular bed of the cat. When tone in the pulmonary vascular bed was raised to a high steady level with the thromboxane mimic U-46619, injections of ANP caused dose-related decreases in lobar arterial pressure. After administration of HS-142-1, an ANP-A- and ANP-B-receptor antagonist, vasodilator responses to ANP were reduced. The nitric oxide (NO) synthase inhibitor Nω-nitro-ω-arginine methyl ester (L-NAME) enhanced ANP vasodilator responses, suggesting that inhibition of NO modulates ANP responses. L-NAME administration with constant 8-bromo-cGMP infusion attenuated the increased vasodilator response to ANP, suggesting that supersensitivity to ANP occurs upstream to activation of a cGMP-dependent protein kinase. In pulmonary arterial rings, ANP produced concentration-related vasorelaxant responses with and without endothelium. Methylened blue, L-NAME, or Nω-monomethyl-ω-arginine did not alter ANP vasorelaxant responses. These data show that ANP supersensitivity observed in the intact pulmonary vascular bed is not seen in isolated pulmonary arterial segments, suggesting that it may only occur in resistance vessel elements. These results suggest that ANP responses occur through activation of ANP-A and/or -B receptors in an endothelium-independent manner and are modulated by NO in resistance vessel elements in the pulmonary vascular bed of the cat.

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bital sodium (30 mg/kg iv). The animals were strapped in the supine position to a fluoroscopic table, and supplemental doses of anesthetic were administered as needed to maintain a uniform level of anesthesia. The trachea was intubated with a cuffed pediatric endotracheal tube, and the animals spontaneously breathed room air enriched with 100% O₂.

Systemic arterial (aortic) pressure was measured from a femoral artery, and intravenous injections were made into a catheter positioned in the inferior vena cava from a femoral vein.

For perfusion of the left lower lobe, a triple-lumen 28-cm-long 6-F balloon perfusion catheter (Arrow International, Reading, PA) was passed under fluoroscopic guidance from an external jugular vein into the artery to the left lower lung lobe. After the animals were given heparin (1,000 U/kg iv), the lobar artery was vascularly isolated by distention of the balloon cuff on the perfusion catheter. The lung lobe was perfused with a perfusion pump (model 1210; Harvard Apparatus, Millis, MA) by way of the catheter lumen beyond the cuff, with blood withdrawn from a femoral artery. The perfusion rate was adjusted so that lobar arterial perfusion pressure approximated mean pressure in the main pulmonary artery and was not changed thereafter. The flow rate ranged from 29 to 51 ml/min. Left atrial pressure was measured with a 6-F double-lumen catheter (Arrow International, Millis, MA) by way of the catheter lumen beyond the cuff, with blood withdrawn from a femoral artery.

Vascular pressures were measured by electronic averaging (Spectromed, Oxnard, CA) zeroed at right atrial level. Left atrial pressure was measured with Statham P23 or Spectromed DTX Plus transducers (Spectromed, Oxnard, CA) zeroed at right atrial level. Mean vascular pressures obtained by electronic averaging were recorded on a Grass recorder (model 7, Grass Instruments, Quincy, MA). Agonists were injected in small volumes (30–100 μl) directly into the perfusion circuit distal to the pump in a random sequence. Sufficient time was permitted between injections (usually 5–20 min) to allow lobar arterial perfusion pressure to return to baseline value.

In the present study, five sets of experiments were carried out. The first set of experiments was undertaken to investigate the hypothesis that ANP produces vasodilation that is mediated by the ANP-A and/or -B receptor. The effects of HS-142-1, an ANP-A and ANP-B-receptor antagonist, on responses to ANP, acetylcholine, isoproterenol, cromakalim, sodium nitroprusside, and prostacyclin were investigated in the pulmonary vascular bed of the cat. When pulmonary lobar vascular resistance was elevated by infusion of the stable prostaglandin analog U-46619, the agonists were injected directly into the perfusion circuit. The second set of experiments was undertaken to investigate the hypothesis that nitric oxide synthesis modulates responses to ANP. In these experiments, vasodilator responses to ANP were compared when lobar arterial pressure was raised with U-46619 alone and when tone was increased by intralobar infusions of U-46619 and 8-bromo-cGMP (8-BrcGMP) was infused into the lobar artery. In these experiments, control responses to vasodilator agents were obtained when lobar arterial pressure was raised to an average of 35 ± 1 mmHg with U-46619. The lobar arterial pressure was permitted to return to near-baseline values before a repeat intralobar infusion of 8-BrcGMP was then started. The infusion rate of 8-BrcGMP, determined in pilot experiments, decreased lobar arterial pressure by ∼5 mmHg. Twenty to thirty minutes after 8-BrcGMP, the infusion of U-46619 was increased sufficiently to raise lobar arterial pressure to 35 ± 2 mmHg, and responses to vasodilator agents were again determined.

The fourth set of experiments was similar to the previous set using a cAMP analog, 8-bromo-cAMP (8-BrcAMP), to investigate the hypothesis that the responses seen with 8-BrcGMP were selective in nature. In the fifth set of experiments, vasodilator responses to ANP, nitroglycerin, and sodium nitroprusside were compared when lobar arterial pressure was raised with U-46619 alone and when tone was increased by the administration of l-NAME followed by a constant intralobar infusion of U-46619 and 8-BrcGMP. In these experiments, lobar arterial pressure averaged 35 ± 1 mmHg in the control period and 34 ± 2 mmHg during the treatment period.

In vitro. For in vitro studies, adult cats of either sex were sedated with ketamine hydrochloride (10–15 mg/kg im) and were anesthetized with pentobarbital sodium (30 mg/kg iv). The cat lungs were quickly removed and immersed in cold (40°C) Krebs-Henseleit (KH) solution (composition in mM: 118 NaCl, 4.7 KCl, 2.5 CaCl₂, 1.2 K₂HPO₄, 25 NaHCO₃, 1.2 MgSO₄, and 10 dextrose). The pulmonary artery was isolated, and excess fat and connective tissue were removed. Vessels were cut into 3- to 5-mm rings and mounted in organ baths containing 10-ml KH solution. Two stainless steel hooks were inserted into the lumen of the pulmonary artery: one was fixed, whereas the other was connected to a transducer. The tissue bath solution was maintained at 37°C and bubbled with a 95% O₂-5% CO₂ mixture. The pulmonary arterial rings were equilibrated for 90 min with three changes of KH solution, and an optimal tension of 2–3 g was applied. Contraction measurements were measured isometrically with force-displacement transducers (FT03; Grass Instruments) and were recorded on a Grass model 7 polygraph. The contractile ability of each ring was then assessed by exposing the ring to 60 mM KCl, and then the ring was washed and allowed to relax to baseline tension. Only when two reproducible contractions could be elicited was the individual ring used in further studies. The integrity of the endothelium was determined by obtaining a maximal vasorelaxant response to acetylcholine. Three sets of experiments were carried out during the in vitro portion of the study. The first set of experiments was undertaken to investigate the hypothesis
that responses to ANP are endothelium independent in pulmonary arteries of the feline. The second set of experiments investigated the hypothesis that ANP produces vasodilation via a soluble guanylate cyclase-independent mechanism; methylene blue (an inhibitor of soluble guanylate cyclase activation) was utilized. The third set of experiments was undertaken to investigate the hypothesis that ANP responses are independent of L-arginine. To investigate the role of nitric oxide in mediating responses to ANP, L-NAME and Nω-monomethyl-L-arginine (L-NMMA; substrate analog) were used. All agents were added directly to the organ bath in a cumulative concentration manner. The concentration of all drugs was reported as the final molar concentration in the organ chamber.

Preparation of drugs and statistics. Acetylcholine chloride, bradykinin, ANP, glycercyl trinitrate, isoproterenol, sodium nitroprusside, 8-BrcGMP, 8-BrcAMP, dibutryl-cAMP (DB-cAMP), and prostacyclin (Sigma Chemical, St. Louis, MO) were dissolved in 0.9% saline. HS-142-1 was dissolved and further dilutions were made in normal saline. Methylene blue (an inhibitor of soluble guanylate cyclase) was dissolved in 100% ethanol at a concentration of 10 mg/ml, and further dilutions were made in normal saline. Methylene blue, L-NAME hydrochloride, and L-NMMA (Sigma Chemical) were dissolved in normal saline immediately before use. Cromakalim (SmithKline Beecham, Sussex, UK) was dissolved in 20% ethanol in saline at a concentration of 1 mg/ml, and further dilutions were made in 0.9% saline.

Blood gases and pH were measured with a Corning model 178 analyzer and were in the normal range. All hemodynamic data are expressed in absolute units and are presented as means ± SE. Responses represent peak changes, unless otherwise noted. These data were analyzed by using a one-way analysis of variance and Scheffe’s F test or a paired t-test. P < 0.05 was the criterion for statistical significance.

RESULTS

Under baseline conditions, when tone in the pulmonary vascular bed was at resting levels (12–15 mmHg), injections of ANP into the perfused lobar artery in doses of 0.1 and 1.0 μg had no significant effect on lobar arterial pressure (data not shown). However, when lobar arterial pressure was raised to a high steady value (35 ± 1 mmHg) with an infusion of U-46619, intralobar injections of ANP in doses of 0.1–1 μg caused significant dose-related decreases in lobar arterial pressure (Fig. 1). Lobar arterial pressure was unchanged at all doses of the peptide studied (data not shown). The effects of the ANP-receptor antagonist HS-142-1 on pulmonary vasodilator responses to ANP were investigated, and these data are also summarized in Fig. 1. The decreases in lobar arterial pressure in response to ANP (0.1–1 μg) under elevated tone conditions were reduced significantly after administration of HS-142-1 in a dose of 10 mg/kg iv (Fig. 1A). The inhibitory effects of the ANP-receptor antagonist on vasodilator responses to ANP were overcome when larger doses of the peptide were administered (Fig. 1A). The duration of the actions of HS-142-1 was assessed by comparing responses to ANP 2 h after administration of the antagonist. There was little, if any, tendency for vasodilator responses to ANP to return toward control 2 h after administration of ANP-receptor blocking agent in a dose of 10 mg/kg iv (Fig. 1B). Pulmonary vasodilator responses to acetylcholine, isoproterenol, cromakalim, sodium nitroprusside, and prostacyclin in these experiments were not altered after administration of HS-142-1, indicating that the ANP-receptor blockade was selective and that responsiveness of the vascular bed did not change over the 2-h period during which responses were studied (data not shown). Administration of HS-142-1 in a dose of 10 mg/kg iv had no significant effect on mean systemic arterial, lobar arterial, or left atrial pressure (data not shown).

The effect of the nitric oxide synthase inhibitor L-NAME on pulmonary vasodilator responses to ANP was investigated, and responses to ANP were compared when tone in the pulmonary vascular bed was increased with U-46619 alone (control) and with U-46619 and L-NAME. When lobar arterial pressure had attained a peak value after administration of L-NAME, the U-46619 infusion was again started, and the infusion rate was adjusted so that an average pressure similar to that obtained during the control period was attained. The administration of L-NAME in a dose of 100 mg/kg iv resulted in a significant increase in the pulmonary vasodilator response to ANP (Fig. 2), nitroglycerin (Fig. 3), and sodium nitroprusside (Fig. 4).
3), whereas no change was seen in response to the endothelium-independent vasodilator agonists cromakalim (data not shown), isoproterenol (data not shown), prostacyclin (data not shown), 8-BrcGMP (Fig. 3), or DBcAMP (Fig. 3). After administration of L-NAME, a significant decrease in vasodilator responses to the endothelium-dependent agonists bradykinin and acetylcholine was observed (data not shown). After administration of L-NAME, the increase in vasodilator response to ANP, nitroglycerin, and sodium nitroprusside was reproducible for up to 30 min and did not show evidence of tachyphylaxis (data not shown).

To investigate the role of the endothelium and the subsequent activation of soluble guanylate cyclase in mediating vasodilator responses to ANP, responses were obtained in isolated feline pulmonary arterial rings with intact endothelium and without endothelium. In the first set of experiments, ANP produced concentration-dependent relaxation of pulmonary arterial rings with and without endothelium precontracted with 15 μM U-46619, suggesting that ANP-induced vasorelaxation is not dependent on the presence of the endothelium (Fig. 4). In a separate set of experiments, the role of soluble guanylate cyclase activation was investigated. In pulmonary arterial rings with intact endothelium precontracted with U-46619, addition of ANP (10^{-9}–10^{-7} M) produced concentration-dependent relaxation (Fig. 5). After administration of methylene blue, responses to ANP were not significantly altered. In the next set of experiments, the influence of two nitric oxide synthase inhibitors on responses to ANP were investigated. After administration of L-NMMA or L-NAME (300 μM), a dose that significantly inhibited endothelial-dependent responses to acetylcholine (data not shown), no significant change in the arterial vasorelaxant response to ANP was observed compared with control (Fig. 6).

In addition to investigating the effects of inhibition of nitric oxide synthase, the role of the endothelium, and the activation of soluble guanylate cyclase, the effects of cGMP-dependent protein kinase activation and of L-NAME on responses to ANP were studied in the pulmonary vascular bed of the cat. In experiments with 8-BrcGMP before L-NAME, vasodilator responses to ANP were compared when tone was increased with U-46619 and, to a similar level, by an infusion of both U-46619 and 8-BrcGMP. During treatment with 8-BrcGMP, decreases in lobar arterial pressure in response to ANP (0.1–1 μg) were not significantly changed compared with responses obtained during the U-46619 infusion in the control period (Fig. 7A). In experiments with 8-BrcGMP in the presence of L-NAME, vasodilator responses to ANP were compared when tone was increased with U-46619 and to a similar level after administration of L-NAME (100 mg/kg iv) with constant infusion of U-46619 and 8-BrcGMP.

Fig. 2. Influence of Nω-nitro-L-arginine methyl ester (L-NAME) on decreases in lobar arterial pressure in response to atrial natriuretic peptide. Responses were compared before (control) and after administration of L-NAME in a dose of 100 mg/kg iv. Values are means ± SE; n, no. of animals. *Significantly different from control, P < 0.05.

Fig. 3. Influence of L-NAME and L-NAME with constant infusion of 8-bromo-cGMP (8-BrcGMP) on decreases in lobar arterial pressure in response to nitroglycerin (GTN; A) and sodium nitroprusside (SNP; B). Responses were compared at similar levels of baseline tone before (control) and after administration of L-NAME and L-NAME with constant infusion of 8-BrcGMP. C: influence of L-NAME on decreases in lobar arterial pressure in response to 8-BrcGMP and dibutyryl-cAMP (DBcAMP). Responses were compared at similar levels of baseline tone before (control) and after administration of L-NAME. Values are means ± SE; n, no. of animals. *Significantly different from control, P < 0.05.
Treatment with L-NAME and 8-BrcGMP did not change the decreases in lobar arterial pressure in response to ANP (0.1–1 μg) compared with responses to ANP during the U-46619 infusion control period (Fig. 7B). However, responses to nitroglycerin and sodium nitroprusside were significantly increased compared with responses obtained in the U-46619 infusion control period (Fig. 3). In similar experiments, the effects of constant infusion of 8-BrcAMP in the presence of L-NAME were also investigated, and vasodilator responses to ANP were compared when tone was increased with U-46619, with L-NAME, and with ANP alone, and responses were compared with those obtained with the baseline U-46619 infusion control period. The results are shown in Fig. 6.

Fig. 4. Influence of endothelial cell removal on the pulmonary vasorelaxant response to atrial natriuretic peptide on feline pulmonary arterial (PA) rings precontracted with U-46619. Values are means ± SE; n, no. of rings from separate animals.

Fig. 5. Influence of methylene blue on the pulmonary vasorelaxant response to atrial natriuretic peptide on feline PA rings precontracted with U-46619. Control, responses without methylene blue. Values are means ± SE; n, no. of rings from separate animals.

Fig. 6. Influence of L-NAME and Nω-monomethyl-L-arginine (L-NMMA) on the pulmonary vasorelaxant response to atrial natriuretic peptide on feline PA rings precontracted with U-46619. Control, response without L-NAME or L-NMMA. Values are means ± SE; n, no. of rings from separate animals.

Fig. 7. A: influence of 8-BrcGMP on decreases in lobar arterial pressure in response to atrial natriuretic peptide. Responses were compared at similar levels of baseline tone before (control) and after infusion of 8-BrcGMP. B: influence of L-NAME and constant infusion of 8-BrcGMP on decreases in lobar arterial pressure in response to atrial natriuretic peptide. Responses were compared at similar levels of baseline tone before (control) and after administration of L-NAME with constant infusion of 8-BrcGMP. Values are means ± SE; n, no. of animals.
The agonist had little agonist activity. Competitive, and long in duration; and that the inhibitory effects of HS-142-1 are selective, -B receptors on undefined resistance vessel elements; the results of previous studies of systemic arterial resistance in the anesthetized rat, of experiments in the pulmonary vascular bed extending the results of studies of systemic arterial pressure in the intact-chest cat. These data are consistent with results of studies in the pulmonary circulation of the cat, lamb, fetal lamb, and rabbit in which nitric oxide synthase inhibitors increased pulmonary vascular resistance (1, 2, 5–8, 13, 20). These studies are consistent with the hypothesis that tonic release of nitric oxide may serve to regulate baseline vascular tone in the pulmonary circulation. In addition to increasing lobar vascular resistance in the cat, L-NAME significantly increased vasodilator responses to ANP, nitroglycerin, and sodium nitroprusside. The enhanced vasodilator response to agents that release nitric oxide is not observed in all models, and the mechanism is uncertain, but it has been hypothesized that the removal of the basal nitric oxide-mediated vasodilator tone in the cardiovascular system leads to a “specific supersensitivity” of soluble guanylate cyclase (13, 15). The results of the present study with nitroglycerin and sodium nitroprusside are consistent with previous studies and with the hypothesis that inhibition of nitric oxide synthesis with agents such as L-NAME will enhance responses to nitrovasodilators. The observation that vasodilator responses to 8-BrcGMP, DBcAMP, cromakalim, isoproterenol, or prostacyclin are not reduced suggests that L-NAME did not alter endothelium-independent responses mediated by agents with increased cGMP or cAMP levels, activate cGMP- or cAMP-dependent protein kinases, stimulate ß-adrenergic or prostacyclin receptors, or open ATP-sensitive potassium channels. Moreover, results demonstrating that vasodilator responses to bradykinin and acetylcholine are reduced by L-NAME suggest that they are mediated in part by the release of nitric oxide and the activation of soluble guanylate cyclase in the pulmonary vascular bed (4, 6, 13).

The results showing that responses to ANP are enhanced after L-NAME administration extend previous observations in certain studies showing enhancement of vasodilator responses to agents that release nitric oxide (13, 15). ANP produces smooth-muscle relaxation through increases in cGMP by activation of ANP-A and/or -B receptors and the subsequent stimulation of particulate guanylate cyclase (11, 25). The observation that responses to ANP are enhanced by nitric oxide synthase inhibitors may suggest that the “supersensitivity” seen with the stimulation of soluble guanylate cyclase after administration of an arginine analog may also be induced by the ANP-stimulated particulate guanylate cyclase in the presence of L-NAME. Furthermore, the observation that responses to ANP are enhanced by nitric oxide synthase inhibitors may suggest that the “supersensitivity” to ANP is selective for the particulate guanylate cyclase pathway and occurs at the level of the ANP-A or -B receptor, membrane-bound guanylate cyclase.

8-BrcGMP is a lipophilic cGMP analog that directly activates cGMP-dependent protein kinase (12). ANP...
responses were not significantly different after admin-
istration of L-NAME with constant infusion of 8-BrcGMP, demonstrating that 8-BrcGMP infusion was able to inhibit the increased vasodilation that was seen after the L-NAME treatment period, whereas con-
stant infusion of 8-BrcGMP alone did not significantly alter responses to ANP. These data further support the hypothesis that the supersensitivity to ANP occurs at a level upstream to cGMP-dependent protein kinase ac-
tivation. During the L-NAME treatment period, re-
sponses to nitroglycerin and sodium nitroprusside were significantly enhanced compared with responses obtained in the control period; however, during con-
stant infusion of 8-BrcGMP with L-NAME, responses to nitroglycerin and sodium nitroprusside were not significantly changed compared with responses in the L-NAME treatment period. These data show that 8-BrcGMP does not have the ability to inhibit the increased vasodilator response seen in response to agents that are nitric oxide donors. The reason for the difference between effects on ANP and on nitroglycerin or sodium nitroprusside is unknown but may be re-
lated to the action of soluble guanylate cyclase in the endothelial cell and the action of particulate guanylate cyclase in the vascular smooth muscle cell.

The results of this study show that ANP relaxed precontracted rings of feline pulmonary artery with and without endothelium and are consistent with previ-
ous studies of the bovine pulmonary circulation and of the systemic circulation of a variety of species (10, 11, 18, 25). Previous reports have shown that ANP causes endothelium-independent relaxation of arteries and cGMP, but not cAMP, accumulation (10). The observation that methylene blue, an inhibitor of solu-
ble guanylate cyclase or superoxide radical inducer (6, 13), failed to alter arterial relaxant responses to ANP is consistent with reports that stimulation of ANP recep-
tors activates the particulate rather than the soluble form of guanylate cyclase and that this activation is methylene blue insensitive.

Previous studies have reported that responses to ANP and ANP receptors exhibit heterogeneity. L-NAME and the arginine analog L-NMMA did not signifi-
cantly alter responses to ANP in precontracted feline pulmonary rings. The reason for the difference in results between the in vitro and in vivo responses of ANP is unknown but may be due to differences in the inhibitory function domain within the ANP receptor (23). These results may suggest a fundamental differ-
ence in response to ANP in the conduit-type pulmonary arterial segment used in vitro and the resistance vessel segments that regulate tone and responses in vivo in the feline pulmonary vascular bed.

In summary, the present results show that, under elevated tone conditions, ANP has potent pulmonary vasodilator activity and that responses to the peptide are blocked in a selective manner by the ANP-receptor antagonist HS-142-1, indicating that responses are mediated by ANP-A and/or -B receptors. The present data show that vasodilator responses to ANP are in-
creased by L-NAME, indicating that inhibition of basal release of nitric oxide modulates responses to ANP. The observation that ANP-induced vasodilator re-
sponses were not enhanced after administration of L-NAME and constant infusion of 8-BrcGMP suggests that supersensitivity to ANP occurs upstream to the activation of cGMP-dependent protein kinase. Further-
more, although the reason for the difference is un-
known, the present data show that the supersensitivity to ANP is not observed in isolated pulmonary arterial segments, suggesting that this supersensitivity may be observed only in resistance vessel elements in the intact pulmonary vascular bed of the cat.

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