Effect of Atrial Natriuretic Peptide and Other Vasoactive Compounds on the Uterine Vascular Bed of the Nonpregnant Sheep (43505)

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Abstract. **It has been reported that atrial natriuretic peptide (ANP) concentrations are elevated in pregnancy and further elevated in pregnancy-induced hypertension. Atrial stretch and volume expansion appear to be important stimuli for ANP release. During normal pregnancy, a striking change in hemodynamics occurs that may increase plasma ANP concentrations. ANP has potent natriuretic, diuretic, and smooth muscle relaxant activities. The biological effects of ANP during pregnancy may play an important role in the physiology and pathophyisology of pregnancy. Because of possible interactions during pregnancy due to secondary effects of maternal cardiovascular changes and physiological adaptation, the present study sought to evaluate and characterize the local effects of atriopeptin II on the uterine vascular bed of the *nonpregnant* sheep. Ewes with catheters in the femoral artery, femoral vein, and uterine artery and electromagnetic flow probes on the middle uterine arteries were monitored for blood pressure (BP), heart rate (HR), and uterine blood flow before and after the administration into the uterine artery of bolus injections of 2, 4, 20, and 40 × 10^{-9} *M* (5, 10, 50, and 100 μg) of the synthetic ANP (atriopeptin II). For comparison purposes, the effects of prostaglandin I_2 in doses of 1.2, 2.5, 12, and 25 × 10^{-8} *M* (5, 10, 50, and 100 μg), vasoactive intestinal polypeptide in doses of 3, 9, 30, 90, 300, and 900 × 10^{-11} *M* (0.1, 0.3, 1, 3, 10, and 30 μg), and bradykinin in doses of 9.4, 28, 94, 280, 940, and 2800 × 10^{-11} *M* (0.1, 0.3, 1, 3, 10, and 30 μg) were also tested. Appropriate vehicles were tested and found to be without effect.**

All four compounds were found to be vasodilators of the nonpregnant uterine vasculature. ANP administered into the uterine artery decreased BP (87 ± 4 mm Hg to 79 ± 4 mm Hg with 50 μg [20 × 10^{-9} *M*]), increased HR (90 ± 5 bpm to 105 ± 4 bpm), and significantly increased uterine blood flow (from 14 ± 3 to 37 ± 4 ml/min with a dose of 100 μg [40 × 10^{-8} *M*, $P < 0.05$]). Prostaglandin I_2 failed to alter BP, but caused significant increases on HR (100 ± 4 to 124 ± 13 bpm, $P < 0.05$) and uterine blood flow (17 ± 4 to 73 ± 10 ml/min, $P < 0.05$). Vasoactive intestinal polypeptide caused a significant tachycardia (97 ± 10 to 158 ± 9 bpm, $P < 0.05$) at the highest dose. Bradykinin increased BP significantly at two of the highest doses. These data indicate that local intra-arterial bolus injections of ANP not only caused local uterine effects, but also had significant effects on BP and HR, which were qualitatively similar to those produced by vasoactive intestinal polypeptide. [P.S.E.B.M. 1992, Vol 201]

Mammalian cardiac atria myocytes contain secretory granules which, under increased intra-atrial pressure and/or atrial stretching, release a group of closely related 21–26 amino acid peptides collectively referred to as atrial natriuretic peptide (ANP). Atrial natriuretic peptide produces vasorelaxation, natriuresis, and diuresis, reduces systemic arterial blood pressure, and has a variable effect on renal blood flow and vascular resistance (1–3).

Human pregnancy is characterized by impressive physiological maternal cardiovascular modifications in hemodynamics: i) The volume of intra- and extravascular body fluids are significantly increased. ii) Cardiac output is increased by up to 40%. iii) The vascular responsiveness to vasoconstrictor agents is known to decrease, as does the peripheral vascular resistance (4).

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The mechanisms that regulate these circulatory responses during pregnancy are still largely unknown. Since atrial stretch consequent to hemodynamic changes or volume expansion appears to be the most important stimulus for atrial natriuretic peptide release (5, 6), the physiological modifications in pregnancy may activate ANP release and alter plasma ANP concentrations.

Some investigators have reported increased concentrations of ANP with pregnancy (7). However, others have reported that vascular resistance does not change with exogenous ANP infusion (8). It is possible that the same impressive maternal cardiovascular modifications in hemodynamics during pregnancy that stimulate ANP release may interact, alter, or mask ANP effects. It is also possible that during pregnancy, the response of the uterine vasculature to endogenous ANP is already maximal. The effects of ANP are thought to be due largely to its renal hemodynamic actions, which include increases in efferent arteriolar tone and glomerular filtration rate (9). Acute bolus intravenous injection of synthetic atrial natriuretic peptide in dogs, sheep, and humans results in an acute fall in systemic arterial blood pressure and a rise in heart rate (10, 11). In both anesthetized as well as unrestrained conscious dogs, ANP induced a decrease in blood pressure (12).

Because of the potential role of ANP in the regulation of cardiovascular hemodynamics, the present study sought to clarify and characterize, in the absence of secondary effects that may be present during pregnancy, the local effects of atriopeptin II (a synthetic 23-amino acid peptide) on the uterine vascular bed of the nonpregnant sheep. In order to contrast the role of ANP in our system to other known vasodilators, the effects of prostaglandin (PG) I_2, vasoactive intestinal peptide (VIP), and bradykinin were also evaluated.

Materials and Methods

Twenty-nine nonpregnant ewes of mixed breeds weighing between 50 and 60 kg were used for this study and were obtained from local suppliers. Food was withdrawn for 48 hr and water withheld for 24 hr prior to surgery. Ewes were sedated intravenously with 10 mg of diazepam (Hoffmann La Roche, Inc., Nutley, NJ) followed by 15 mg/kg of pentobarbital sodium (The Butler Co., Columbus, OH) before 15 mg of a hyperbaric spinal anesthesia (1% Tetracaine HCl; Winthrop Pharmaceuticals, New York, NY). Supplemental doses of pentobarbital sodium were administered as needed for sedation. Animals were secured in the supine position and draped aseptically. The femoral artery and vein were isolated and cannulated with polyvinyl catheters and advanced to the level of the distal aorta and inferior vena cava, respectively. A 15-cm incision was made through the midline in order to expose the uterus. Uterine blood flow was measured by use of a square-wave electromagnetic flow probe (RF1000; Dienco, Los Angeles, CA) placed around the left and right main uterine arteries in the broad ligament. The lateral branch of the uterine artery distal to the first bifurcation was also isolated and cannulated with polyvinyl catheters for infusion of vasoactive substances. All catheters and cables were exteriorized via a subcutaneous tunnel and stored in a canvas bag attached to the skin on the side of the sheep.

Antibiotics (25 mg/kg, Combiotics; G. C. Hanford Manufacturing Co., Syracuse, NY) were administered on the day of surgery and 3 days postoperatively. The animals were placed in portable stainless steel cages and given food and water *ad libitum*. All ewes were allowed a 5- to 7-day recovery period in which uterine blood flow was monitored daily. Catheters were flushed daily with heparinized saline (1000 μg/ml) to maintain patency.

Experimental Protocol

All 29 ewes were randomized into one of four groups: Group 1 animals ($n = 7$) received a bolus injection of ANP (Atriopeptin II; Sigma Chemical Co., St. Louis, MO) at doses of 2, 4, 20, and 40×10^{-9} M (5, 10, 50, and 100 μg). Group 2 animals ($n = 11$) received similar bolus injections of PGI_2 (PGI_2 Na in 0.1 M Tris buffer, pH 9.4; Cayman Chemical Co., Ann Arbor, MI) at doses of 1.2, 2.5, 12, and 25×10^{-8} M (5, 10, 50, and 100 μg). Group 3 animals ($n = 6$) received bolus injections of bradykinin (Sigma) at doses of 9.4, 28, 94, 280, 940, and 2800×10^{-11} M (0.1, 0.3, 1, 3, 10, and 30 μg), while Group 4 ($n = 5$) received similar bolus injections of VIP (Sigma) at doses of 3, 9, 30, 90, 300, and 900×10^{-11} M (0.1, 0.3, 1, 3, 10, and 30 μg). The choice of a large range of doses for each compound was specifically designed to allow differentiation between the local effects of low doses on the uterine vasculature from the systemic effects of higher doses.

Arterial blood pressure was measured by means of a Micron MP-15 blood pressure transducer (Micron Instruments, Los Angeles, CA) anchored at the level of the sternum and connected to the maternal femoral artery catheter. Heart rate was recorded by use of a Sensormedic cardiotachometer (Sensormedic Instruments, Fullerton, CA) triggered by an arterial pressure pulse. On the day of the experiment, blood pressure, heart rate, and blood flow were recorded on a Sensormedic dynograph (R612 physiological recorder) for 30 min before the administration of any compound in order to establish baseline values. After a 30-min baseline period, ANP, PGI_2, bradykinin, or VIP was injected into the uterine artery as a bolus injection at randomly assigned doses. All parameters were allowed to return to baseline (between 40 and 75 min) before the next dose was given. Only one vasoactive substance was injected per day. Thereafter, changes in blood pressure, heart rate, uterine blood flow (UBF), and vascular

resistance were determined. The ability to increase the flow in the target vessel was considered a valid interpretation of the effects of ANP and its ability to influence vessel tonicity.

Calculations

Uterine vascular resistance was calculated using the following formula: UVR = mean arterial blood pressure/uterine blood flow. All results are expressed as mean ± SE. Paired observations (before and after) were analyzed by paired *t* test in order to assess the statistical significance of differences between measurements. *P*-values ≤ 0.05 were considered statistically significant. Analysis of variance and the Newman-Keuls test were used for dose-response comparison (differences between individual means). *P*-values ≤ 0.05 were considered significant.

Results

Effect of ANP. The local administration of ANP (atriopeptin II) into the uterine artery resulted in a significant increase in uterine blood flow. The peak response ($P = 0.05$) in UBF (from a baseline of 14 ± 3 to 37 ± 4 ml/min) occurred with a dose of 40×10^{-9} *M* (100 μg; Fig. 1). The local administration of ANP into the uterine artery increased HR with all doses and reached significance ($P = 0.05$) at the doses of 20 and 40×10^{-9} *M* (50 and 100 μg, respectively; Table I). Local intra-arterial bolus injections of ANP in the uterine vasculature produced significant ($P = 0.05$) decreases in vascular resistance with all doses (Table I), and mean arterial blood pressure reached significance ($P = 0.05$) at the doses of 20 and 40×10^{-9} *M* (50 and 100 μg, respectively; Table I).

Effect of PGI_2. The local administration of PGI_2 into the uterine artery resulted in a significant ($P = 0.05$) elevation of heart rate with doses of 12 and 25×10^{-8} *M* (50 and 100 μg; Table I), and significant ($P = 0.05$, Newman-Keuls) dose-related increases in UBF, which reached a peak (79 ± 8 ml/min) at a dose of 12×10^{-8} *M* (50 μg, Fig. 1). PGI_2 decreased vascular resistance, but failed to modify systemic arterial blood pressure (Table I).

Effect of VIP. Local VIP administration into the uterine artery produced a significant ($P = 0.05$, Newman-Keuls) dose-related increase in UBF that reached a maximum of 100 ± 19 ml/min, over baseline (Fig. 2). HR increased and reached significance ($P = 0.05$, Newman-Keuls) at 90×10^{-11} *M* (3.0 μg) and above (Table II). VIP did not alter systemic arterial blood pressure at any dose (Table II). However, the low uterine vascular resistance (as an effect of high baseline uterine blood flow, 26.5 ± 0.7 ml/min) was further significantly reduced with each dose (Table II, $P <$ 0.05).

Effect of Bradykinin. The local administration of bradykinin into the uterine artery produced a significant ($P = 0.05$, Newman-Keuls) dose-related increase in UBF (Fig. 2). The maximal effect occurred with a dose of 280×10^{-11} *M* (3.0 μg, $P = 0.05$, Newman-Keuls). Bradykinin, also produced a significant ($P =$ 0.05, Newman-Keuls) dose-related increase in HR (Table II), and significantly ($P < 0.05$) increased systemic arterial blood pressure at doses of 380 and 940×10^{-11} *M* (3.0 and 10 μg, respectively). Blood pressure did not change significantly at the lower concentrations of 9.4, 28, and 94×10^{-11} *M* (0.1, 0.3, and 1.0 μg, respectively; Table II). However, uterine vascular resistance was significantly ($P < 0.05$) decreased when bradykinin was injected into the uterine artery ($P < 0.05$; Table II) at any dose level.

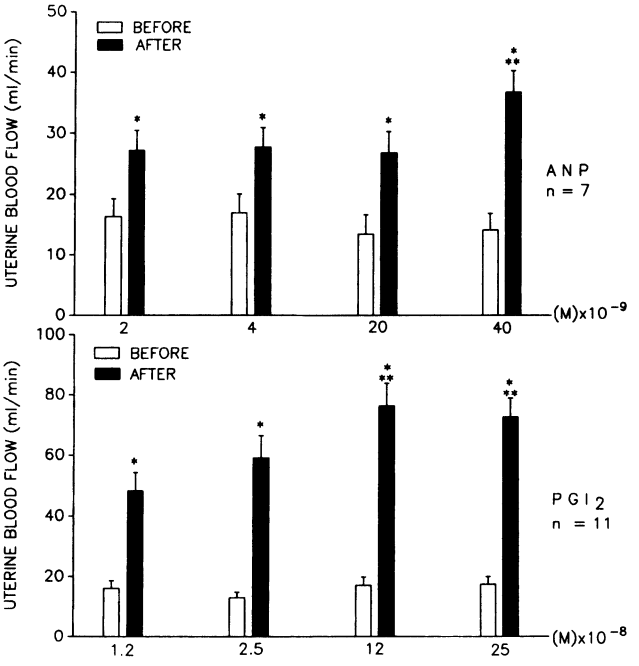

Figure 1. Uterine blood flow before and after the administration of bolus injections of (A) 2, 4, 20, and 40×10^{-9} *M* (5, 10, 50, and 100 μg, respectively) of ANP ($n = 7$) and (B) 1.2, 2.5, 12, and 25×10^{-8} *M* (5, 10, 50, and 100 μg, respectively) of PGI_2 ($n = 11$). Data are expressed as mean ± SE. * $P < 0.05$, after versus before. ** Between means, $P = 0.05$, Newman-Keuls.

Dose-response curves for the effects of intra-arterial bolus injections of ANP, PGI_2, VIP, and bradykinin on the uterine blood flow are shown in Figure 3. ANP was found to be considerably less potent a uterine vasodilator than PGI_2, VIP, and bradykinin.

Discussion

Numerous investigators have reported that mammalian atrial cardiocytes contain multiple forms of natriuretic polypeptide associated with specific atrial granules that show morphological resemblance to secretory granules in peptide hormone-producing cells (4, 5). Atrial natriuretic polypeptide has been reported to relax vascular smooth muscle cells *in vitro* and to decrease blood pressure in intact animals (11, 12).

Table I. Systemic Effects of ANP and PGI_2[a]

	Blood pressure (mm Hg)		Heart rate (bpm)		Uterine vascular resistance (mm Hg/ml/min)	
	Before	After	Before	After	Before	After
ANP (10^{-9} *M*)						
2	86 ± 4	84 ± 4	92 ± 4	95 ± 4	6.4 ± 1.1	3.4 ± 0.4[b]
4	87 ± 4	85 ± 4	91 ± 5	100 ± 3	6.6 ± 1.5	3.3 ± 0.4[b]
20	87 ± 4	79 ± 4[b]	90 ± 5	105 ± 4[b]	6.7 ± 3.5	3.3 ± 0.4[b]
40	82 ± 2	78 ± 3[b]	94 ± 5	106 ± 5[b]	8.6 ± 2.5	2.4 ± 0.3[b,c]
PGI_2 (10^{-8} *M*)						
1.2	89 ± 4	89 ± 4	89 ± 8	96 ± 8	7.4 ± 0.7	2.6 ± 0.3[b]
2.5	89 ± 4	93 ± 4	88 ± 8	103 ± 8	8.5 ± 1.6	2.5 ± 0.5[b]
12	90 ± 3	89 ± 5	87 ± 8	112 ± 11[b]	7.4 ± 1.0	1.5 ± 0.3[b]
25	92 ± 5	85 ± 7	100 ± 4	124 ± 13[b]	8.1 ± 2.9	1.9 ± 0.4[b]

[a] Data are expressed as mean ± SE.
[b] $P < 0.05$, after versus before.
[c] Between means, $P = 0.05$ Newman-Keuls.

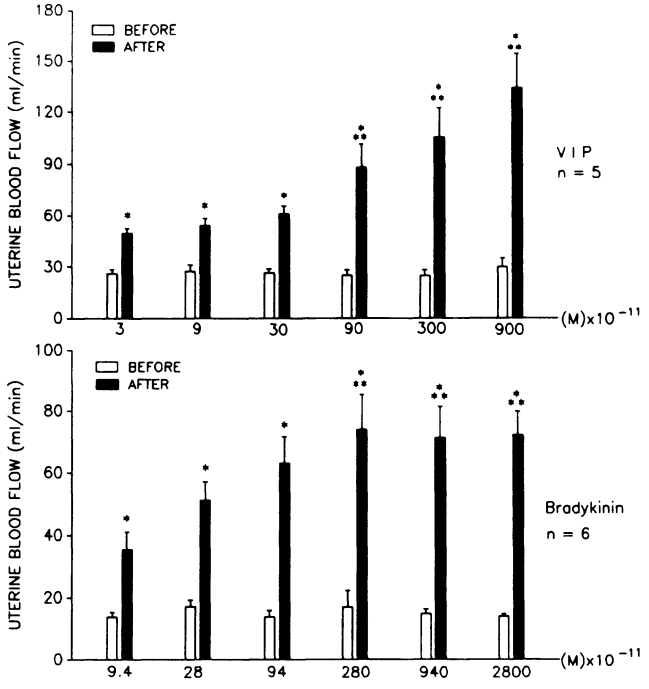

Figure 2. Upper and lower panel: Uterine blood flow before and after the administration into the uterine vascular bed of bolus injections of (A) 3, 9, 30, 90, 300, and 900 × 10^{-11} *M* (0.1, 0.3, 1, 3, 10, and 30 μg, respectively) of VIP ($n = 5$) and (B) 9.4, 28, 94, 280, 940, and 2800 × 10^{-11} *M* (0.2, 0.3, 1, 3, 10, and 30 μg, respectively) of bradykinin ($n = 6$). Data are expressed as mean ± SE. * $P < 0.05$, after versus before. ** Between means, $P = 0.05$, Newman-Keuls.

The present study was undertaken in order to define the specific effects of ANP on the uterine vascular bed. Nonpregnant animals were used in order to avoid the multiplicity of confounding variables related to pregnancy that may otherwise interfere with uterine responsiveness to ANP and obscure its specific effects. We may have used pharmacological concentrations of ANP, since much lower concentrations have been reported in pregnant sheep (13). However, these concentrations were used in order to ensure a maximal vascular response to ANP administration.

In our study, intrauterine arterial bolus administration of ANP (atriopeptin II) produced an increase in uterine blood flow in nonpregnant ewes secondary to uterine vasodilation. The potency of ANP *was not* comparable to that of bradykinin, PGI_2, or VIP and may be a consequence of the short half-life of ANP in plasma (14). This observation may be interpreted to indicate that the hormonal system is adapted to regulate rapid responses to changes in physiological parameters, such as intravascular volume expansion (15). In pregnant sheep, vascular resistance did not change after the infusion of ANP into the uterine artery (8). The observation that ANP did not change vascular resistance in pregnant animals may be interpreted to indicate possible interactions during pregnancy due to secondary effects of maternal cardiovascular changes, i.e., maximally dilated vessels.

Bradykinin has been previously shown to be a potent uterine vasodilator (16). The present experiments demonstrate that bradykinin also increased systemic arterial blood pressure and heart rate. These systemic effects may be mediated by bradykinin-induced release of catecholamine, since the systemic effects are totally abolished by an α- and β-adrenergic receptor blockade (16). In our study, VIP, bradykinin, and PGI_2 were also found to be potent vasodilators of the uterine vasculature of the nonpregnant sheep.

The observation that ANP decreased systemic arterial blood pressure (highest two doses) may be a reflection that peripheral as well as uterine vasodilation occurred. ANP and VIP produced significant increases in heart rate with the peak change occurring at 20 × 10^{-9} *M* (50 μg), and 900 × 10^{-11} *M* (30 μg), respectively. The tachycardia that occurred concomitantly with the decrease in blood pressure may be explained by compensatory excitation of the sympathetic nervous system in response to peripheral vasodilation.

Table II. Systemic Effects of VIP and Bradykinin[a]

	Blood pressure (mm Hg)		Heart rate (bpm)		Uterine vascular response (mm Hg/ml/min)	
	Before	After	Before	After	Before	After
VIP (10^{-11} *M*)						
3	90 ± 5	84 ± 5	96 ± 9	102 ± 10	3.6 ± 0.5	1.9 ± 0.1[b]
9	88 ± 6	85 ± 4	99 ± 9	105 ± 9	3.5 ± 0.5	2.0 ± 0.1[b]
30	89 ± 7	88 ± 7	92 ± 10	107 ± 8	3.6 ± 0.5	1.8 ± 0.1[b]
90	88 ± 6	80 ± 7	92 ± 10	132 ± 11[b,c]	3.8 ± 0.5	1.2 ± 0.1[b,c]
300	90 ± 6	83 ± 9	101 ± 11	140 ± 8[b,c]	4.3 ± 1.2	1.0 ± 0.1[b,c]
900	88 ± 6	78 ± 6	97 ± 10	158 ± 9[b,c]	3.4 ± 0.7	0.7 ± 0.1[b,c]
Bradykinin (10^{-11} *M*)						
9.4	90 ± 3	92 ± 5	107 ± 6	119 ± 1[b]	7.0 ± 0.7	3.1 ± 0.8[b]
28	92 ± 4	95 ± 6	104 ± 5	114 ± 3[b]	5.7 ± 0.8	2.0 ± 0.2[b]
94	90 ± 4	97 ± 4	107 ± 5	120 ± 5[b]	7.4 ± 1.2	1.7 ± 0.2[b]
280	89 ± 4	101 ± 7[b]	109 ± 4	124 ± 4[b]	7.4 ± 1.6	1.5 ± 0.3[b,c]
940	92 ± 4	109 ± 8[b]	110 ± 3	130 ± 7[b,c]	6.9 ± 1.3	1.7 ± 0.3[b,c]
2800	87 ± 8	103 ± 15	101 ± 5	153 ± 10[c]	6.3 ± 0.4	1.5 ± 0.2[b,c]

[a] Data are expressed as mean ± SE.
[b] $P < 0.05$, after versus before.
[c] Between means, $P = 0.05$ Newman-Keuls.

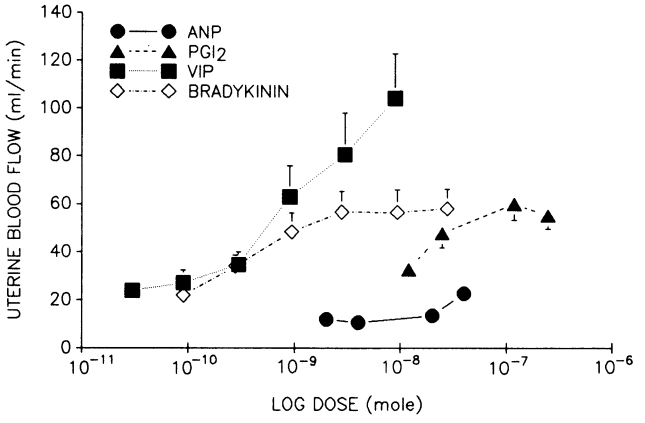

Figure 3. Comparison of dose (mole)-response curves for the effects of a bolus injection of ANP, PGI_2, VIP, and bradykinin on uterine blood flow. Data are expressed as mean ± SE. (Data generated by subtraction of the baseline UBF.)

The vasodilator properties of ANP have been ascribed to a direct action of the peptide on vascular smooth muscle cells (17). However, it is still debated whether the fall in blood pressure resulting from ANP administration is mediated by a direct action of the peptide on vascular smooth muscle cells, because the hypotensive effect of ANP has been shown by some investigators to occur in the presence of a decreased cardiac output (18). There is some evidence to suggest that ANP exerts a suppressive effect on renin release (19). Therefore, it is possible that the hypotensive effect of ANP is related to the peptide-induced reduction in the activity of renin-angiotensin system. In this context, the ability to increase the flow in the target vessel (UBF) was considered valid interpretation of the effect of ANP and its ability to influence vessel tonicity. ANP may significantly influence, either directly or indirectly, major points of control for blood pressure including renal sodium and water excretion, vessel tonicity, aldosterone production, heart rate, cardiac output, renin secretion, and arginine vasopressin release (20–22).

In summary, intra-arterial local bolus administration of ANP, VIP, PGI_2, and bradykinin resulted in significant uterine vasodilation in the nonpregnant sheep. ANP was the weakest of the vasodilators tested, but did produce decreases in systemic arterial blood pressure and increases in HR. These cardiovascular effects of ANP in the nonpregnant sheep are consistent with those of an endogenous antihypertensive agent.

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