Role of Nitric Oxide in Mediating In Vivo Vascular Responses to Calcitonin Gene-Related Peptide in Essential and Peripheral Circulations in the Fetus

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Background—The role of calcitonin gene-related peptide (CGRP) in cardiovascular regulation is gaining clinical and scientific interest. In the adult, in vivo studies have shown that CGRP-stimulated vasodilation in several vascular beds depends, at least in part, on nitric oxide (NO). However, whether CGRP acts as a vasodilator in the fetus in vivo and whether this effect is mediated via NO have been addressed only minimally. This study tested the hypothesis that CGRP has potent NO-dependent vasodilator actions in essential and peripheral vascular beds in the fetus in late gestation.

Methods and Results—Under anesthesia, 5 fetal sheep at 0.8 gestation were instrumented with vascular catheters and Transonic flow probes around an umbilical artery and a femoral artery. Five days later, fetuses received 2- and 5-μg doses of exogenous CGRP intra-arterially in randomized order. Doses were repeated during NO blockade with the NO clamp. This technique permits blockade of de novo synthesis of NO while compensating for tonic production of the gas, thereby maintaining basal cardiovascular function. CGRP resulted in potent and long-lasting NO-dependent dilation in the umbilical and femoral circulations, hypotension, and a positive cardiac chronotropic effect. During NO blockade, the femoral vasodilator response to CGRP was diminished. In contrast, in the umbilical vascular bed, the dilator response was not only prevented but reversed to vasoconstriction.

Conclusions—CGRP has potent NO-dependent vasodilator actions in fetal essential and peripheral vascular beds. CGRP-induced NO-dependent effects in the umbilical vascular bed may provide an important mechanism in the control and maintenance of umbilical blood flow during pregnancy. (Circulation. 2005;112:2510-2516.)

Key Words: calcitonin gene-related peptide  fetus  hemodynamics  nitric oxide  vasodilation

Calcitonin gene-related peptide (CGRP) is a 37–amino acid peptide that was discovered in 1983 by alternative processing of RNA transcripts from the calcitonin gene.1 It is synthesized primarily in sensory neurones of the dorsal root and trigeminal ganglia,2 which, in turn, extend axons centrally to the spinal cord and peripherally to various organs, including blood vessels. In the vasculature, terminals from these neurones innervate the smooth muscle layer,3 and neuronal activation causes the release of CGRP, which induces a powerful nonadrenergic, noncholinergic vasodilation. This potent dilator action of CGRP and the wide distribution of perivascular neurones containing CGRP throughout the cardiovascular system suggest that CGRP is in a prime position to regulate blood flow under physiological conditions.

In the adult, several mechanisms have been proposed for CGRP-induced vasodilation. In vitro studies have suggested either the activation of adenylate cyclase,4 resulting in the opening of ATP-sensitive K⁺ channels (K⁺_ATP)5 in the vascular smooth muscle, or the release of nitric oxide (NO) from vascular endothelial cells.6,7 The finding that CGRP receptors are present on both the endothelium and smooth muscle cells of the vasculature further supports the concept that the actions of CGRP are mediated by pathways involving both endothelium-dependent and -independent mechanisms.8,9 However, in vivo studies favor the proposal that the vasodilator actions of CGRP are mediated, at least in part, by NO-dependent pathways and not by activation of K⁺_ATP channels.10

The increased maternal plasma levels of CGRP during pregnancy,11 its presence in human cord and neonatal blood, and the finding that the concentration of CGRP in fetal serum correlates with both fetal weight and gestational age12 indicate a functional role for CGRP in prenatal life. This is further supported by evidence from Dong and colleagues,13,14 who have demonstrated the presence of components of the CGRP receptor in the vascular endothelium and smooth muscle cells of human fetoplacental vessels, and by Terenghi and colleagues,15 who have detected CGRP within the human nervous system during the first trimester of pregnancy. However, little is known about the actions of CGRP in the fetal vasculature. In the present study, we have tested the hypo-
esis that CGRP has important NO-dependent vasodilator actions in fetal essential and peripheral vascular beds. The hypothesis was tested by investigating the in vivo effects of exogenous doses of CGRP before and during NO blockade on changes in umbilical (UBF) and femoral (FBF) blood flow measured by indwelling transonic flow probes in the unanesthetized late-gestation ovine fetus surgically prepared for long-term recording.

Methods

Surgical Preparation

All procedures were performed under the UK Animals (Scientific Procedures) Act 1986 and were approved by the Ethical Review Committee of the University of Cambridge. Five Welsh Mountain sheep fetuses were surgically instrumented for long-term recording at 120±2 days of gestation (term is ~145 days) under strict aseptic conditions as previously described in detail.16 In brief, food, but not water, was withheld from the pregnant ewes for 24 hours before surgery. After induction with 20 mg/kg IV sodium thiopentone (Intraval Sodium, Merial Animal Health Ltd), general anesthesia (1.5% to 2.0% halothane in 50:50 O2:N2O) was maintained with positive pressure ventilation. Midline abdominal and uterine incisions were made; the fetal hind limbs were exteriorized; and on one side, femoral arterial (internal diameter, 0.86 mm; outer diameter, 1.52 mm; Critchly Electrical Products) and venous (internal diameter, 0.56 mm; outer diameter, 0.96 mm) catheters were inserted. The catheter tips were advanced carefully to the descending aorta and inferior vena cava, respectively. Another catheter was anchored onto the fetal hind limb for recording of the reference amniotic pressure. In addition, a transit-time flow transducer was implanted around the contralateral femoral artery (2R or 3S, Transonic Systems Inc) and around one of the umbilical arteries, close to the common umbilical artery inside the fetal abdominal cavity (4SB, Transonic Systems Inc).17 The uterine incisions were closed in layers; the dead space of the catheters was filled with heparinized saline (80 IU heparin per 1 mL in 0.9% NaCl) and the catheter ends were plugged with sterile brass pins. The catheters and flow probe leads were then exteriorized via a keyhole incision in the maternal flank and kept inside a plastic pouch sewn onto the maternal skin.

Postoperative Care

During recovery, ewes were housed in individual pens in rooms with a 12-hour/12 hour light/dark cycle. Here, they had free access to hay and water and were fed concentrates twice daily (100 g sheep nuts No. 6, H&C Beart Ltd). Antibiotics were administered daily to the ewe (0.20 to 0.25 mg/kg IM Depocillin, Mycofarm), to the fetus intravenously, and into the amniotic cavity (1.5% to 2.0% halothane in 50:50 O2:N2O) was maintained with positive pressure ventilation. Midline abdominal and uterine incisions were made; the fetal hind limbs were exteriorized; and on one side, femoral arterial (internal diameter, 0.86 mm; outer diameter, 1.52 mm; Critchly Electrical Products) and venous (internal diameter, 0.56 mm; outer diameter, 0.96 mm) catheters were inserted. The catheter tips were advanced carefully to the descending aorta and inferior vena cava, respectively. Another catheter was anchored onto the fetal hind limb for recording of the reference amniotic pressure. In addition, a transit-time flow transducer was implanted around the contralateral femoral artery (2R or 3S, Transonic Systems Inc) and around one of the umbilical arteries, close to the common umbilical artery inside the fetal abdominal cavity (4SB, Transonic Systems Inc).17 The uterine incisions were closed in layers; the dead space of the catheters was filled with heparinized saline (80 IU heparin per 1 mL in 0.9% NaCl) and the catheter ends were plugged with sterile brass pins. The catheters and flow probe leads were then exteriorized via a keyhole incision in the maternal flank and kept inside a plastic pouch sewn onto the maternal skin.

Experimental Protocol

After at least 5 days of postoperative recovery, all fetuses received 2- and 5-μg bolus doses of CGRP (β-CGRP, C-1044, Sigma Chemicals) dissolved in heparinized saline via the femoral artery catheter in a randomized order. Doses were injected over 2 to 3 seconds and were administered after at least 15 minutes of stable baseline recording. The CGRP doses were chosen from our own pilot experiments and from a previous study by Takahashi and colleagues.18 In that study, treatment of late-gestation fetal sheep with a similar dose of CGRP produced a marked vasodilation in the pulmonary vascular bed. In the present study, exogenous doses of CGRP were first given during a slow intravenous infusion of vehicle (80 IU heparin per 1 mL in 0.9% NaCl) and then repeated during blockade of NO with the NO clamp, a technique that is well established in our laboratory.17,19 The NO clamp permits blockade of de novo synthesis of NO while compensating for the tonic production of the gas, thereby maintaining basal cardiovascular function. In brief, a bolus dose (100 mg/kg bolus dissolved in 2 mL heparinized saline) of Nω-nitro-L-arginine methyl ester (L-NAME; Sigma Chemicals) was injected via the femoral artery catheter. This was immediately followed by fetal intravenous infusion (5.1±0.8 μg·kg⁻¹·min⁻¹, mean±SD, dissolved in heparinized saline) with the NO donor sodium nitroprusside (SNP; Sigma Chemicals, UK) to return fetal arterial blood pressure, heart rate, UBF, and FBF to pretreatment levels. At the end of the experimental protocol, the effectiveness of NO blockade by the clamp and the persistence of L-NAME in the system were tested by withdrawal of the SNP infusion. A day later, the ewes and fetuses were humanely killed with a lethal dose of sodium pentobarbitone (200 mg/kg IV Pentoject, Animal Ltd). The positions of the implanted catheters and flow probes were confirmed, and the fetuses were weighed.

Blood Sampling Regimen

Before each experimental protocol, descending aortic blood samples (0.3 mL) were taken using sterile techniques from the fetus to determine arterial blood gas and acid base status (ABL8 Blood Gas Analyzer, Radiometer; measurements corrected to 39.5°C). Values for percentage saturation of hemoglobin with oxygen and blood hemoglobin concentration were determined with a hemoximeter (OSM2, Radiometer). In addition, blood glucose and lactate concentrations were measured by an automated analyzer (Yellow Springs 2300 Stat Plus Glucose/Lactate Analyser, YSI Ltd).

Data and Statistical Analyses

Umbilical vascular conductance (UVC) and femoral vascular conductance (FVC) were calculated by use of Ohm’s principle by dividing mean blood flow (UBF or FBF) by mean corrected arterial blood pressure. All measured variables were then analyzed for normality of distribution and expressed as mean±SEM. For each dose response of CGRP, baseline values for all cardiovascular variables measured were obtained by averaging the data over the 60 seconds preceding the administration of each bolus dose. The change in all cardiovascular variables to each dose of CGRP was first analyzed for significance in relation to its own baseline, during either saline infusion or NO blockade, using the significance of single measurement comparisons between treatment (saline versus NO clamp), dose (2 versus 5 μg), or interaction between treatment and dose were assessed statistically with 2-way repeated-measures ANOVA (Sigma-Stat, SPSS Inc). When a significant effect of time or group was indicated, the post hoc Tukey test was used to isolate the statistical differences. Differences in all cardiovascular variables during and after removal of the NO clamp were analyzed with Student t test for paired data. For all comparisons, statistical significance was accepted at P<0.05.

Results

Fetal Arterial Blood Gas and Metabolic Status

Fetal arterial blood gas and metabolic status measured before each experimental protocol were within normal ranges for
Figure 1. Cardiovascular responses to CGRP before and during NO blockade. Bars represent the mean±SEM for the changes in arterial blood pressure, heart rate, FBF, FVC, UBF, and UVC in response to 2- and 5-μg doses of CGRP before (■; n=5) and during (●; n=5) NO blockade with the NO clamp. Significant differences: *P<0.05, difference from own baseline (significance of a single mean test); **P<0.05, 2 vs 5 μg CGRP; ***P<0.05, before vs during NO blockade (2-way repeated-measures ANOVA with post hoc Tukey test).

Welsh Mountain sheep at 125 days of gestation: pH, 7.33±0.01; ABE, 1.0±0.1 mEq/L; HCO₃⁻, 25.7±0.1 mEq/L; PₐCO₂, 54.4±1.2 mm Hg; PₐO₂, 22.3±1.2 mm Hg; saturation, 54.8±3.2%; hemoglobin, 10.5±0.6 g/dL; lactate, 0.77±0.06 mmol/L; and glucose, 0.87±0.05 mmol/L. Neither treatment with CGRP nor fetal exposure to the NO clamp affected basal arterial blood gas or metabolic status.

Arterial Blood Pressure and Heart Rate Responses
CGRP (2 and 5 μg) produced a dose-dependent decrease in fetal arterial blood pressure (−7.6±0.8 and −11.8±1.2 mm Hg) and increase in fetal heart rate (66±8 and 106±5 bpm; P<0.05; Figure 1). During NO blockade, hypotension (−1.9±1.2 and −5.3±1.4 mm Hg) and tachycardia (20±6 and 31±6 bpm) were markedly diminished by both doses of CGRP (P<0.05; Figure 1), with the alteration in arterial blood pressure to 2 μg CGRP showing no significant change from its own baseline (P>0.05). CGRP also produced a dose-dependent effect on the duration of the hypotensive (10.6±1.3 and 15.6±1.5 minutes) and tachycardic (11.6±1.3 and 21.4±2.0 minutes; P<0.05; Figure 2) responses, each of which was significantly shortened during NO blockade (P<0.05; Figure 2).

Umbilical Hemodynamics
CGRP (2 and 5 μg) produced similar increases in UBF (102±8 and 113±7 mL/min) and UVC [1.83±0.17 and 2.26±0.19 (mL · min⁻¹) · mm Hg⁻¹]. During NO blockade, umbilical vasodilation was reversed to vasoconstriction in response to both doses of exogenous CGRP [UBF, −50±16 and −49±4 mL/min; UVC, −0.78±0.24 and −0.65±0.11 (mL · min⁻¹) · mm Hg⁻¹; P<0.05; Figure 1]. CGRP also produced a dose-dependent effect on the duration of the umbilical vasodilator response (14.2±2.3 and 19.9±1.4 minutes). This was significantly shortened after reversal to the vasoconstrictor response during NO blockade (6.9±0.8 and 8.6±0.7 minutes; P<0.05; Figure 2).

Femoral Hemodynamics
CGRP (2 and 5 μg) produced similar increases in FBF (19±2 and 23±3 mL/min) and FVC [0.35±0.05 and 0.47±0.06 (mL · min⁻¹) · mm Hg⁻¹]. During NO blockade, the femoral vasodilation to 2 μg of CGRP was abolished [FBF, 6±2 mL/min; FVC, 0.14±0.07 (mL · min⁻¹) · mm Hg⁻¹; P<0.05] and markedly diminished to 5 μg CGRP [FBF, 11±1 mL/min; FVC, 0.25±0.04 (mL · min⁻¹) · mm Hg⁻¹; P<0.05; Figure 1]. CGRP also produced a dose-dependent effect on the duration of the femoral vasodilator response (12.3±1.3 and 17.6±1.5 minutes); this was significantly shortened during NO blockade (8.0±1.5 and 7.9±1.3 minutes; P<0.05; Figure 2).

An example of the individual cardiovascular responses to 5 μg CGRP before and during NO blockade with the NO clamp is shown in Figure 3.

Removal of the NO Clamp
Withdrawal of the SNP infusion led to a significant increase in fetal arterial blood pressure (Δ12.8±1.4 mm Hg) and to
decreases in fetal heart rate (∆=38±8 bpm) and vasoconstriction in both the femoral [FVC, ∆=0.32±0.06 (mL·min⁻¹)·mmHg⁻¹] and umbilical [UVC, ∆=1.65±0.27 (mL·min⁻¹)·mmHg⁻¹; P<0.05] vascular beds (Figure 4). This provided evidence for the effectiveness of NO blockade by the clamp and the persistence of the action of L-NAME within the system until the end of the experimental protocol.

Discussion

The results of the present study show that fetal treatment with CGRP elicits potent and long-lasting vasodilator actions in the fetal umbilical and femoral vascular beds, hypotension, and a positive cardiac chronotropic effect. During NO blockade, not only were these cardiovascular responses to CGRP significantly reduced, but the umbilical dilator response was

Figure 3. Example of the cardiovascular responses to CGRP before and during NO blockade. An individual example of the response in arterial blood pressure, heart rate, FBF, FVC, UBF, and UVC to 5 μg CGRP before and during NO blockade with the NO clamp.

Figure 4. Effect of NO clamp removal on cardiovascular variables. Values represent the mean±SEM calculated every 30 seconds for arterial blood pressure, heart rate, FBF, FVC, UBF, and UVC in response to removal of the NO clamp (arrow). Significant difference: *P<0.05, during vs removal of the NO clamp (Student t test for paired data).
reversed to vasoconstriction. These data support the hypothe-
sis that CGRP has important NO-dependent vasodilator
actions in essential and peripheral vascular beds in the
late-gestation ovine fetus.

CGRP is one of the most potent vasodilator peptides
known,20 having a potency of ~10-fold greater than prostag-
lansins and ~100- to 1000-fold greater than classic vasodi-
lators such as acetylcholine, adenosine, and 5-HT.21 Results
from the present study support the current literature and show
for the first time that in the fetus, in vivo treatment with
CGRP has potent dilator actions in the umbilical and femoral
vascular beds. Furthermore, fetal treatment with CGRP
resulted in hypotension and a positive cardiac chronotropic
effect, which, unlike the vascular responses, showed significa-
cant dose-dependent effects. Hypotension is likely to be
the result of vasodilation in several vascular beds in the fetus,
leading to a reduction in total peripheral vascular resistance
and thus a fall in arterial blood pressure at a given cardiac
output. The positive cardiac chronotropic effect may be elici-
ted by a baroreflex response to hypotension. However, it
is also likely to involve the direct effects of the peptide on
CGRP receptors, which have been reported to be present in
both adult and fetal hearts.18,22 The CGRP receptors have
recently been cloned and are characterized as 7 transmem-
brane G protein–coupled calcitonin receptor-like receptors,
which are associated with 1 of 3 single transmembrane
spanning receptor activity modifying proteins (RAMP1, RAMP2, RAMP3). The RAMPs interact via their NH2
terminus23 with the calcitonin receptor-like receptors to pro-
duce a different receptor specificity by influencing the for-
mation of the receptor pocket by allosteric modulation.24 The
biological actions of CGRP are mediated predominantly
through the CGRP1 receptor, which is made up of the
calcitonin receptor-like receptors and RAMP1 proteins, both
of which have been demonstrated within the endothelium
and underlying smooth muscle cells of human fetoplacental
vessels.13,14

Unlike classic vasodilators, CGRP elicited cardiovascular
responses, which were particularly long-lasting. CGRP has a
half-life of ~7 to 10 minutes in the adult circulation,25 and its
vasodilator activity is removed after clearance by several
mechanisms, including those involving mast cell tryptase,26
neutral endopeptidases,27 matrix metalloproteinase-2,28 or
reuptake mechanisms into the sensory nerve terminal after
repolarization.29 The duration of all cardiovascular responses
showed a significant dose-dependent effect, clearly attributed
to the increased circulating concentration of CGRP at higher
doses and hence the increased time required for metabolic
disposition.

To assess the contribution of NO to the mechanisms of
action and clearance of CGRP, each dose of CGRP was
repeated during NO blockade with the NO clamp. This
technique permits blockade of de novo synthesis of NO while
compensating for the tonic production of the gas, thereby
maintaining basal cardiovascular function.17,19,30 Results from
the present study show that during NO blockade, there were
marked reductions in both the magnitude and duration of all
cardiovascular responses measured to increasing exogenous
doses of CGRP. In peripheral vascular beds in the fetus, the
dilator response to low doses of CGRP was totally abolished
during NO blockade, suggesting that at low concentrations,
the actions of CGRP are completely mediated via mecha-
nisms involving NO-dependent pathways. In contrast, at
higher doses of CGRP, NO-independent mechanisms may
become recruited to mediate the much reduced but persistent
femoral vasodilator actions of the peptide during NO block-
ade. For example, CGRP has been shown to stimulate
adenylate cyclase,2 which, in turn, will increase cAMP
concentrations. This will activate protein kinase A and hence
lead to the phosphorylation and opening of K+ATP channels,
resulting in hyperpolarization and relaxation of the arterial
smooth muscle.5 Accordingly, an elegant study by Takahashi
and colleagues18 has reported that in another fetal “periphe-
ral” circulation, the pulmonary vascular bed, CGRP increases
pulmonary blood flow via its specific receptor in part through
NO release and in part through K+ATP channel activation.

In essential fetal vascular beds such as the umbilical
circulation, several studies have shown that NO has an
important role in the mechanisms regulating blood flow
during basal and stimulated conditions.17,31 A recent study by
Dong and colleagues34 demonstrated that CGRP antagonism
in vitro diminished the dilator actions of exogenous CGRP in
the human fetoplacental vasculature. Furthermore, Thakor
and Giussani32 have shown that CGRP antagonism in vivo
diminished the umbilical hemodynamic defense response to
acute hypoxemia in the ovine fetus. The results of the present
in vivo study extend these findings to show that the potent
dilator action of CGRP in the umbilical vascular bed of the
ovine fetus is mediated exclusively by NO because, in
contrast to the femoral vascular bed, dilatation was not only
diminished but reversed to vasoconstriction during NO block-
ade. CGRP is known to increase noradrenergic and adrener-
gic sympathetic outflow after activation of various hypotha-
lamic nuclei.33–35 Thus, it is possible that constriction of the
umbilical vascular bed after exogenous CGRP during NO
blockade may be mediated via activation of adrenoreceptors
in the umbilical vasculature.36 an effect that clearly is
overridden by the potent NO-dependent actions of the peptide
in this essential vascular bed. Alternatively, constrictor ac-
tions of CGRP during NO blockade may be similar to those
of acetylcholine in vessels once denuded of the endothelium
or in intact vessels after NO synthase blockade, as elegantly
demonstrated by Furchgott and Zawadzki37 and Librizzi and
colleagues.38 These effects of vasodilator agents after NO
blockade may be secondary to the release of other vasoactive
agents such as thromboxane, as shown for acetylcholine by
Tsujii and Cook.39

The difference in the pattern of the vascular responses to
CGRP after NO blockade between essential and peripheral
vascular beds may be attributed to whether these vessels
respond to the peptide in an endothelium-dependent or
-independent manner.40,41 Previous studies have reported that
in large conduit vessels such as the aorta, the majority of the
actions of CGRP are endothelium dependent, involving
the release of NO.40,42 Hence, it is no surprise that in the
umbilical artery, in essence an extension of the descending
aorta in the fetus, the actions of CGRP are largely dependent
on NO. In contrast, the femoral vasculature appears to be able
to recruit other NO-independent mechanisms after NO blockade, consistent with evidence that CGRP has endothelium-independent actions in more peripheral circulations, as reported for the isolated rat caudal artery and rabbit mesenteric artery.

The diminished cardiac positive chronotropic effect of CGRP during NO blockade is likely due to a baroreflex of reduced gain in response to a smaller fall in arterial blood pressure. Alternatively, NO may also be involved in the mechanisms by which CGRP directly affects cardiac pacemaker activity. In the heart, the influx of calcium resulting from the transmembrane calcium current $I_{Ca}$ has a fundamental role in pacemaker activity. Furthermore, it has recently been shown that in isolated frog single heart cells, CGRP dramatically increases $I_{Ca}$ by mechanisms that cannot be blocked by $\beta$-adrenergic antagonists. However, whether this novel CGRP-mediated neurogenic control of cardiac pacemaker activity involves NO-dependent pathways is unknown.

The results of the present study also show that NO blockade reduced the duration of all cardiovascular effects of CGRP, implying that NO may act to inhibit the mechanism mediating the metabolic disposition of the peptide. Although information on the effects of NO on most mechanisms of clearance of CGRP is unavailable, it is known that in adult rats, NO downregulates matrix metalloproteinase-2 in aortic vessels and that inhibition of endogenous NO enhances the release of matrix metalloproteinase-2 in the heart.

In conclusion, the data show that fetal treatment with exogenous CGRP resulted in potent NO-dependent vasodilator actions in the umbilical and femoral vascular beds, hypotension, and a positive cardiac chronotropic effect. CGRP-induced dilatation in peripheral vascular beds involves both NO-dependent and -independent pathways. In contrast, the powerful dilator effects of CGRP in essential vascular beds such as the umbilical circulation appear to be mediated exclusively by NO-dependent pathways. CGRP-induced NO-dependent effects in the umbilical vascular bed may provide an important mechanism in the control and maintenance of UBF during pregnancy.

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References
Pregnancies complicated by chronic adverse intrauterine conditions show an enhanced umbilical vasodilator response to acute hypoxic stress, of the type that may occur during labor and delivery, which may help to protect the compromised fetus. The nature of this mechanism to enhance dilation in the umbilical circulation appears to involve the actions of NO and calcitonin gene-related peptide. Here, we confirm that the umbilical circulation is highly sensitive to the NO-dependent actions of calcitonin gene-related peptide in such a way that when NO is blocked, the dilator actions of the peptide on the umbilical circulation are not only prevented but are reversed to constriction. Combined, past and present evidence suggests an important role for calcitonin gene-related peptide in the maintenance of umbilical blood flow during late gestation in normal and compromised pregnancies.
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