Structure of Cerebral Arterioles in Mice Deficient in Expression of the Gene for Endothelial Nitric Oxide Synthase

Gary L. Baumbach, Curt D. Sigmund, Frank M. Faraci

Abstract—We examined effects of pharmacological inhibition of nitric oxide synthase (NOS) and genetic deficiency of the endothelial isoform of NOS (eNOS) on structure and mechanics of cerebral arterioles. We measured pressure, diameter, and cross-sectional area (CSA) of the vessel wall (histologically) in maximally dilated cerebral arterioles in mice that were untreated or treated for 3 months with the NOS inhibitor, Nω-nitro-L-arginine methyl ester (L-NAME; 10 mg/kg per day in drinking water). Treatment with L-NAME increased systemic arterial mean pressure (SAP; 143 ± 4 versus 121 ± 4 mm Hg, \( P < 0.05 \)) and CSA (437 ± 27 versus 310 ± 34 μm², \( P < 0.05 \)). These findings suggest that hypertension induced in mice by NOS inhibition is accompanied by hypertrophy of cerebral arterioles. To determine the role of the eNOS isoform in regulation of cerebral vascular growth, we examined mice with targeted disruption of one (homozygous) or both (homozygous) genes encoding eNOS. Wild-type littermates served as controls. SAP and CSA were significantly increased in homozygous (SAP, 141 ± 5 versus 122 ± 3 mm Hg in wild-type mice, \( P < 0.05 \); CSA, 410 ± 18 versus 306 ± 15 μm² in wild-type mice, \( P < 0.05 \)), but not in heterozygous (SAP, 135 ± 4 mm Hg; CSA, 316 ± 32 μm²) eNOS-deficient mice. Carotid ligation normalized cerebral arteriolar pulse pressure did not prevent increases in CSA in homozygous eNOS-deficient mice. Thus, cerebral arterioles undergo hypertrophy in homozygous eNOS-deficient mice, even in the absence of increases in arteriolar pulse pressure. These findings suggest that eNOS plays a major role in regulation of cerebral vascular growth. (Circ Res. 2004;95:000-000.)

Key Words: hypertension ■ L-NAME ■ endothelial nitric oxide synthase deficiency ■ vascular hypertrophy

Small resistance arteries and arterioles undergo hypertrophy in several models of chronic hypertension. Several determinants apparently contribute to vascular hypertrophy, including increases in arterial pressure, particularly pulse pressure, sympathetic nerves, genetic factors, the renin-angiotensin system, and the endothelium-derived contractile factor, endothelin. Another determinant that may contribute to vascular hypertrophy during chronic hypertension is nitric oxide (NO). This suggestion is based on the following observations. First, it has been observed that vasodilator drugs that generate NO inhibit mitogenesis and proliferation of vascular muscle in culture. Second, we have found that hypertension induced in rats with the nitric oxide synthase (NOS) inhibitor, Nω-nitro-L-arginine methyl ester (L-NAME), produced hypertrophy of cerebral arterioles, even when increases in cerebral arteriolar pulse pressure were attenuated with unilateral carotid ligation. These observations suggest that in addition to regulation of resting vascular resistance, NO may play an important role in regulation of vascular structure.

A major limitation of using NOS inhibitors to study the role of NO in cerebral vascular hypertrophy is that most of these agents nonselectively inhibit all isoforms of NOS. Multiple isoforms of NOS may be expressed within the vessel wall, and there are no known selective inhibitors of NOS. For example, in addition to the endothelial isoform of NOS (eNOS), neuronal NOS (nNOS) is expressed in vascular muscle. Furthermore, both perivascular nerves and brain tissue contain large amounts of nNOS, and nNOS has been shown to influence cerebral vascular tone and may therefore also influence cerebral vascular growth. Thus, regardless of the outcome of studies using a NOS inhibitor, no definitive conclusions regarding its effects on cerebral vascular structure and mechanics can be drawn in relation to the specific isoforms of NOS involved. Mice with targeted disruption of the gene encoding for eNOS provide an opportunity to examine the role of eNOS in complex physiological systems. Through studies performed in eNOS-deficient mice, the role of eNOS can be defined without relying on pharmacological inhibitors that lack specificity for NOS isoforms.

The first goal of this study was to examine effects of chronic treatment with L-NAME on structure and mechanics
of cerebral arterioles in mice. Based on our previous findings
in rats treated with L-NAME,14 we anticipated that cerebral
arterioles in L-NAME–treated mice would undergo hypertro-
phy. The second goal was to test the hypothesis that cerebral
arterioles undergo hypertrophy in mice lacking the gene for
eNOS. In addition to providing an approach for examining
the role of the eNOS isoform in cerebral vascular structure
and mechanics, using eNOS-deficient mice in this study also
addresses other potential limitations of L-NAME treatment.
For example, NOS inhibitors may stimulate vascular hyper-
trophy through an interaction with angiotensin II AT1
receptors.22–24

Materials and Methods

Animals
Experiments were conducted on male C57BL/6J mice and male and
female eNOS-deficient mice. Animals were allowed free access to
food and tap water, housed at 25°C, and exposed to 12 hours of light
each day. Procedures followed in this study were in accordance with
institutional guidelines for care and use of experimental animals at
the University of Iowa.

1-NAME–Treated Mice
Male C57BL/6J mice were obtained from Jackson Laboratories. To
evaluate effects of inhibition of NO synthase on cerebral arterioles,
mice were treated with L-NAME (1 g/L) in the drinking water
beginning at 4 weeks of age. Mice that drank tap water served as
controls. Water intake in the L-NAME–treated group was ~200
mL/kg per day. Thus, intake of L-NAME during the treatment period
was ~200 mg/kg per day. Cerebral arterioles were examined after
~3 months of treatment.

eNOS-Deficient Mice

eNOS-deficient mice were produced as described previously.21 We
generated enos−/−, enos+/−, and enos+/+ mice by interbreeding
enos−/− mice that had been derived from 7 to 9 generations of
backcross breeding to C57BL/6J mice. This approach allowed us to
use enos−/− littermates as controls. With littermate controls, any
heterogeneity in genetic background, on average, will be similar in
both control and genetically altered mice. We included the study of
enos−/− mice, because it has been observed previously that vascular
responses to some stimuli are altered in enos−/− mice.25,26 In
addition, experts in the field of genetics encourage the study of
heterozygous deficient mice because, depending on the results, they
may encourage the study of genetic polymorphisms in humans.27

Genotyping of the animals was performed by Southern blotting or
polymerase chain reaction from tail biopsy specimens as previously
described.28–30

To determine whether effects of eNOS deficiency on cerebral arterioles
resulted from increases in arterial pressure, separate groups of
eNOS−/− and eNOS+/- mice (obtained from Jackson Laboratories)
underwent unilateral carotid ligation at 4 weeks of age. Mice were
anesthetized with Avertin (0.2 to 0.3 mL, intraperitoneally), shaved,
and prepared with a 70% alcohol solution, and a ligature was tied
tightly around the left common carotid artery. To control for possible
damage to sympathetic nerves by the carotid ligature, a second
ligature was tied loosely around the right carotid artery.

In Vivo Preparation

We examined structure of cerebral arterioles in 6-month-old L-
NAME–treated mice and 6-month-old enos-deficient mice. Be-
cause anesthesia can lower arterial pressure in mice, particularly in
mice with chronic hypertension, we measured systemic arterial
pressure in conscious mice using a method we have described
previously.30,31 After measurement of conscious arterial pressure,
animals were weighed and anesthetized with sodium pentobarbital (5
mg 100 g−1 body weight intraperitoneally), intubated, and mechan-
ically ventilated with room air and supplemental O2. Additional
anesthesia (1.7 mg 100 g−1 body weight intravenous) was adminis-
tered when pressure to a paw evoked a change in blood pressure or heart
rate.

A catheter was inserted into a femoral vein for injection of drugs
and fluids. A catheter was inserted into a femoral artery to record
systemic arterial pressure and obtain blood samples for measurement
of arterial blood gases, and a catheter was inserted into the other
femoral artery to withdraw blood to produce hypotension (needed for
studies of vascular mechanics).

Measurement of Cerebral Arteriolar Pressure
and Diameter

We measured pressure and diameter in first-order arterioles on the
cerebrum through an open skull preparation that we have described in
detail previously.30,31 In mice with unilateral carotid ligation, a dam of acrylic
was constructed along the exposed portion of the superior sagittal suture, and craniotomies were made over parietal
cortex of the left and right cerebral hemispheres. Cerebral arteriolar
systolic, diastolic, mean, and pulse pressures were measured continu-
ously with a micropipette connected to a servo-null pressure-measuring device (model 5; Instrumentation for Physiology and
Medicine, Inc.).

Arterioles were monitored through a microscope connected to a
closed-circuit video system and with a magnification of ×356. Images of arterioles were digitized using a video frame grabber
installed in a Macintosh computer (Quadra 900; Apple Computer).

Arteriolar diameter was measured from the digitized images by the
use of image analysis software (NIH Image; National Institutes of
Health, Research Services Branch, NIMH).

Experimental Protocol

Approximately 20 to 30 minutes after completion of surgery,
measurements of cerebral arterioles were obtained under baseline
conditions. Vascular smooth muscle was then deactivated by suffu-
sion of cerebral vessels with artificial cerebral spinal fluid containing
EDTA (67 mmol/L), which produces complete deactivation of
smooth muscle in cerebral arterioles.33 Pressure–diameter relation-
ships were obtained in deactivated cerebral arterioles between
cerebral arteriolar pressures of 40 and 10 mm Hg. Maximally dilated
arterioles were fixed at physiological pressure in vivo by suffusion of
vessels with glutaraldehyde fixative (2.25% glutaraldehyde in 0.10
mol/L cacodylate buffer) while maintaining cerebral arteriolar pres-
sure at baseline levels. Arterioles were considered to be adequately
fixed when blood flow through the arteriole had ceased. After the
anesthetized animal was euthanized by an injection of sodium
pentobarbital, the arteriolar segment used for pressure–diameter
measurements was removed, processed for electron microscopy, and
embedded in Spurr low-viscosity resin while maintaining cross-
sectional orientation. Cross-sectional area of the arteriolar wall was
determined histologically using a method we have described in detail
previously.30,33

Statistical Analysis

Analysis of variance was used to compare systemic mean pressure,
arteriolar pressures, diameters, cross-sectional area of the vessel
wall, and slope of tangential elastic modulus versus stress. Probabi-
ity values were calculated using a Student t test. Statistics were
determined using JMP statistics software (SAS Institute Inc) on a
Macintosh computer.

Results

1-NAME–Treated Mice

Systemic mean arterial pressure was significantly greater in
1-NAME–treated mice than in untreated mice in both the
unanesthetized and anesthetized states, even though anesthe-
sia significantly reduced systemic mean arterial pressure in
both groups (Table 1). Cerebral arteriolar systolic, diastolic,
mean, and pulse pressures were significantly greater in L-NAME–treated mice than in untreated mice (Table 1). Diameter before deactivation with EDTA was not significantly different in cerebral arterioles of mice treated with L-NAME than in untreated mice (Table 1). During deactivation with EDTA, internal and external diameters and cross-sectional area of the vessel wall were greater in cerebral arterioles in mice treated with L-NAME than in cerebral arterioles in untreated mice (Table 1). Thus, during L-NAME–induced hypertension in mice, cerebral arterioles underwent hypertrophy of the vessel wall.

Vascular Mechanics
Internal diameter in cerebral arterioles during maximal dilatation was larger in L-NAME–treated mice than in untreated mice at all levels of arteriolar pressure between 10 and 40 mm Hg (Figure 1, left panel). The stress–strain curve in cerebral arterioles in L-NAME–treated mice was similar to the curve in cerebral arterioles in control mice (Figure 1, right panel). In addition, the slope of tangential elastic modulus versus stress was not significantly different in L-NAME–treated mice and untreated mice (Table 1). These findings suggest that L-NAME–induced hypertension was not accompanied by alterations in passive distensibility of cerebral arterioles, despite hypertrophy of the vessel wall.

eNOS-Deficient Mice
Systemic mean arterial pressure was significantly greater in male and female homozygous eNOS-deficient mice than in male and female wild-type mice in both the unanesthetized

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<th>TABLE 1. Baseline Values in L-NAME–Treated Mice</th>
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<td>Parameter</td>
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<td>Before deactivation of smooth muscle</td>
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<td>Systemic arterial mean pressure, mm Hg</td>
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<td>Cerebral arteriolar pressure, mm Hg</td>
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<td>Cross-sectional area of vessel wall, μm²</td>
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Measurements of internal diameter before deactivation of smooth muscle were obtained at prevailing levels of arterial pressure.
Measurements of internal diameter after deactivation of smooth muscle were made at an arteriolar mean pressure of 40 mm Hg.
Values of external diameter after deactivation of smooth muscle were calculated from measurements of internal diameter at 40 mm Hg arteriolar pressure and histological measurements of cross-sectional area of the vessel wall.
ET vs stress: slope of tangential elastic modulus (ET) vs stress.
Values are mean±SEM in 5 untreated mice and 7 L-NAME–treated mice.
*P<0.05 versus untreated.

Figure 1. Pressure–internal diameter (left panel) and stress–strain relationships (right panel) in cerebral arterioles during maximal dilatation with EDTA in untreated (n=5) and L-NAME–treated mice (n=7). Values are mean±SEM. *P<0.05 versus untreated. D indicates cerebral arteriolar diameter; D₀, original cerebral arteriolar diameter.
Effects of Carotid Ligation

Carotid ligation significantly reduced both mean and pulse pressures in cerebral arterioles in wild-type and homozygous eNOS-deficient mice (Figure 2). Mean pressure in ligated cerebral arterioles was significantly greater in homozygous eNOS-deficient mice than in wild-type mice, whereas pulse pressure ipsilateral to the ligation was not significantly different in the 2 groups. Thus, carotid ligation reduced pulse pressure more effectively than mean pressure in cerebral arterioles of homozygous eNOS-deficient mice.

Cross-sectional area of the vessel wall was significantly less in ligated than in sham arterioles in wild-type mice (Figure 2). In contrast, cross-sectional was not significantly different in sham and ligated arterioles in homozygous eNOS-deficient mice (Figure 2). Thus, carotid ligation in homozygous eNOS-deficient mice did not prevent hypertro-
phy of cerebral arterioles, even though it normalized arteriolar pulse pressure.

**Vascular Mechanics**

Internal diameter in cerebral arterioles during maximal dilation was larger in male and female homozygous eNOS-deficient mice, but not in male and female heterozygous eNOS-deficient, than in male and female wild-type mice at all levels of arteriolar pressure between 10 and 40 mm Hg (Figure 3). The stress–strain curves in cerebral arterioles in male and female homozygous and male and female heterozygous eNOS-deficient mice were similar to the curve in cerebral arterioles in male and female wild-type mice (Figure 4). In addition, the slope of tangential elastic modulus versus stress was not significantly different in male and female homozygous and male and female heterozygous eNOS-deficient mice and male and female wild-type mice (Table 2). These findings suggest that eNOS deficiency in mice was not accompanied by alterations in passive distensibility of cerebral arterioles.

![Figure 2](image2.png)

**Discussion**

There were 3 major new findings in this study. First, chronic hypertension induced by treatment with L-NAME resulted in hypertrophy of cerebral arterioles of C57BL/6J mice. Second, hypertrophy of cerebral arterioles developed in mice with homozygous eNOS deficiency. Furthermore, unilateral carotid ligation in homozygous eNOS-deficient mice did not prevent hypertrophy in cerebral arterioles, and it normalized arteriolar pulse pressure, but not mean pressure. These findings suggest that eNOS deficiency promotes cerebral arteriolar hypertrophy independently of increases in arterial pulse pressure. Previous studies using models of chronic reduction in blood flow and mechanical injury of the vessel wall in eNOS-deficient mice have provided direct evidence that eNOS inhibits vascular growth. The findings in this study support this concept. Furthermore, by using an approach that does not alter cerebral blood flow or directly injure the cerebral arteriolar wall, this study provides direct evidence that eNOS inhibits vascular growth independently of blood flow or mechanical injury. Third, in contrast to homozygous eNOS deficiency, hypertrophy in cerebral arterioles did not develop in mice with heterozygous eNOS deficiency. This finding indicates that deletion of 1 copy of the eNOS gene is not sufficient to induce cerebral arteriolar hypertrophy. In addition, the finding may be relevant to humans with polymorphisms in the eNOS gene, which have been reported to alter the baseline production or bioavailability of NO.

Cerebral arterioles undergo hypertrophy in several models of experimental hypertension, including SHRSP, SHR, and renal hypertension. Determinants that may contribute to cerebral vascular hypertrophy during chronic hypertension include increases in pressure, neurohumoral factors, genetic factors, and endothelial factors, such as release of endothelin.

Another endothelium-derived product that may contribute to regulation of vessel growth is NO. Consideration for this possibility first emerged with the finding that NO suppresses mitogenesis and proliferation of vascular muscle in tissue culture. However, studies in which NO synthase inhibitors were used to suppress production of NO in living animals have yielded conflicting results with respect to the impor-
tance of NO in vascular growth. Dunn and Gardiner found that treatment with L-NAME produced no change in cross-sectional area of the vessel wall in mesenteric resistance arteries in Brattleboro rats. Although Schiffrin et al. found an increase in cross-sectional area of the vessel wall in mesenteric resistance arteries in L-NAME-treated rats, the increase was smaller in magnitude (Δcross-sectional area [CSA] of ~7% to 10%) than that found by other investigators in other models of hypertension that have levels of arterial pressure similar to those in rats treated with L-NAME, such as SHR (ΔCSA of ~70%) and renal hypertensive rats (ΔCSA of ~40%). In contrast, we found in a previous study that treatment of rats with L-NAME resulted in an increase in cross-sectional area of the vessel wall in cerebral arterioles, and the magnitude was greater (ΔCSA of ~50% to 80%) than in small mesenteric arterioles and was similar to, or greater than, increases found in cerebral arterioles in other models of hypertension that have similar increases in arterial pressure, including SHR (ΔCSA of ~58%), SHRSP (ΔCSA of ~30%), and renal hypertensive rats (ΔCSA of ~43%).

The present study confirms our previous findings in rats. Treatment with L-NAME resulted in hypertrophy of cerebral arterioles in mice. Furthermore, the magnitude of cerebral arteriolar hypertrophy induced in mice by L-NAME treatment (ΔCSA of ~40%) was similar to the magnitude induced in rats, even though increases in systemic arterial pressure were considerably less in L-NAME–treated mice (Δsystemic arterial mean pressure [SAP] of ~18%) than in L-NAME–treated rats (ΔSAP of ~65%). Thus, the findings in this study, together with our previous study, suggest that inhibition of NO synthase, with chronic hypertension, may produce substantial hypertrophy in the cerebral circulation. Furthermore, the findings also support the concept that NO may play an important role in the regulation of vascular growth.

At least 3 potential problems complicate interpretation of the effects of L-NAME treatment on vascular structure. First, one must consider the possibility that L-NAME promotes vascular hypertrophy through a mechanism unrelated to its effects on NOS inhibition. For example, L-NAME may stimulate hypertrophy directly or indirectly through activation of angiotensin II AT1 receptors. The second potential problem is that treatment with L-NAME produces significant hypertension in rats and mice. One must consider, therefore, the possibility that hypertrophy of cerebral arterioles in L-NAME–treated animals results directly from increases in arterial pressure per se rather than a nonpressor effect of L-NAME. A third potential problem with L-NAME treatment is that NOS inhibitors, including L-NAME, nonselectively inhibit all isoforms of NOS. In addition to eNOS in endothelium, nNOS is expressed in vascular muscle. Furthermore, perivascular nerves and brain tissue contain large amounts of nNOS, and nNOS has been shown to influence cerebral vascular tone and may therefore also influence cerebral vascular growth. Thus, even if the other potential problems associated with L-NAME treatment can be eliminated, its nonspecificity means that no conclusions regarding effects of L-NAME on cerebral vascular growth can be drawn with respect to which of the NOS isoforms are involved.

We addressed the potential problems with L-NAME treatment in this study by examining cerebral arterioles in eNOS-deficient mice. Our finding that cerebral arterioles in homozygous eNOS-deficient mice undergo hypertrophy supports the concept that eNOS plays a major role in regulation of cerebral vascular growth. The findings also support the suggestion that hypertension induced with L-NAME treatment is related to its effects of NO synthase inhibition rather than its effects on arterial pressure or AT1 receptors.

An important consideration in this study is whether hypertension of cerebral arterioles in homozygous eNOS-deficient mice resulted directly from increases in arterial pressure per se. To test this possibility, we examined effects of unilateral carotid ligation, which we previously found to normalize pulse pressure and prevent hypertrophy in cerebral arterioles of SHRSP. In this study, carotid ligation did not prevent hypertrophy of cerebral arterioles in homozygous eNOS-deficient mice, even though increases in arterial pulse pressure were prevented. However, carotid ligation failed to normalize mean pressure in cerebral arterioles. Thus, we cannot rule out the possibility that hypertension in cerebral arterioles of homozygous eNOS-deficient mice was the result of increases in mean pressure. There are 3 reasons to consider this possibility less likely, however. First, as demonstrated in this study, carotid ligation significantly reduced cross-sectional area of the arteriolar wall in wild-type mice, even though the reduction in arteriolar pulse pressure was less in wild-type mice (~5 mm Hg) than in eNOS-deficient mice (~11 mm Hg). Second, carotid ligation prevents cerebral arteriolar hypertrophy in SHRSP, even though ligation only partially attenuates increases in arteriolar systolic and mean pressures. Finally, arteriovenous fistulae in rats increases pulse pressure, but not mean pressure, in cerebral arterioles, and results in hypertrophy of the arteriolar wall.

We were surprised in this study to find that cerebral arteriolar hypertrophy did not develop in heterozygous eNOS mice. We found previously that responses of carotid artery to acetylcholine, nitrouprusside, and serotonin are altered in heterozygous eNOS-deficient mice, although to a lesser degree than in homozygous eNOS-deficient mice. Based on this finding, we anticipated that some degree of cerebral arteriolar hypertrophy might develop in heterozygous, as well as homozygous, eNOS-deficient mice, although possibly to a lesser extent than in the homozygous group. Cross-sectional area of the vessel wall, however, was virtually the same in cerebral arterioles of heterozygous eNOS-deficient mice and wild-type mice. Thus, in contrast to the apparent "dosing" effect of the eNOS gene on some vascular responses, deletion of a single copy of the eNOS gene is not sufficient to induce cerebral arteriolar hypertrophy.

The mechanism by which NO formed by eNOS may contribute to cerebral vascular growth and hypertrophy is unclear and may involve a number of possibilities. One possibility is that NO affects vascular growth through regulation of endothelin-1 gene expression in the vessel wall. This suggestion is based on the finding that treatment with L-NAME results in increases in severity of hypertension in aorta and large mesenteric arteries in SHRSP together with...
increases in endothelin-1 mRNA in the vessel wall.\textsuperscript{47} In contrast, neither severity of hypertrophy nor endothelin-1 mRNA is increased in small mesenteric resistance arteries of SHRSP during treatment with 1-NAME.\textsuperscript{48} These findings suggest that 1-NAME stimulates production of endothelin-1 in large, but not small, arteries, and thus results in additional hypertrophy only in large arteries as a consequence of the trophic effects of endothelin-1.\textsuperscript{49,50} Based on this assumption, one might conclude that in this study, endothelin-1 did not contribute to hypertrophy of cerebral arterioles in 1-NAME–treated rats. However, we are unaware of any evidence to indicate that 1-NAME does not increase endothelin-1 mRNA in cerebral arterioles. Thus, one cannot rule out a role for endothelin-1 in the development of cerebral arteriolar hypertrophy during treatment with 1-NAME.

Another possible mechanism linking NO to vascular growth involves platelet-derived growth factor (PDGF). PDGF is a powerful growth factor for vascular muscle.\textsuperscript{51,52} PDGF apparently exerts its growth effects in part through the protein kinase B cascade.\textsuperscript{53} Recent evidence suggests that NO selectively attenuates PDGF-induced increases in protein kinase B-\(\alpha\) activation, which in turn may contribute to diminished proliferation of vascular muscle.\textsuperscript{54} Thus, NO may contribute to inhibition of vascular growth by inactivating PDGF-induced growth of vascular muscle. Correspondingly, reduced availability of NO may contribute to vascular hypertrophy by increased PDGF activity.

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References


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