Oxidized Low-Density Lipoprotein Enhances Myogenic Tone in the Rabbit Posterior Cerebral Artery Through the Release of Endothelin-1

Hui Xie, MD, PhD; John A. Bevan, MD

Background and Purpose—Cerebral arteries develop stretch-induced myogenic tone, which plays an important role in the regulation of blood flow to the brain. Although the effect of oxidized LDL (Ox-LDL) on many aspects of the vascular endothelial and smooth muscle cell function have been extensively investigated, its influence on myogenic activity has not been studied.

Methods—The effect of Ox-LDL on the myogenic tone that develops in the perfused rabbit posterior cerebral artery at intramural pressures between 40 and 90 mm Hg was examined.

Results—Ox-LDL (10 \( \mu \)g/mL) significantly enhanced myogenic tone by 21.4\( \pm \)6.1% to 28.5\( \pm \)1.8% at 60 to 90 mm Hg pressure (\( P \), 0.05) but had no influence on norepinephrine- (0.5 to 1 \( \mu \)mol/L) and KCl (20 mmol/L)–induced constriction. Ox-LDL was effective whether the artery was exposed to it from the intraluminal or the extraluminal surface. Lysophosphatidylcholine (10 \( \mu \)mol/L), a lipid component of Ox-LDL, had an equivalent potentiating effect. Native LDL (100 \( \mu \)g/mL) was inactive. The myogenic tone–potentiating effect of Ox-LDL was abolished by endothelium removal but was not influenced by the NO synthase inhibitor \( \text{N}^\text{G} \)-nitro-\( \text{L} \)-nitro-arginine methyl ester (50 \( \mu \)mol/L). This effect was reversed by the endothelin-1 (ET-1) antagonist BQ-123 (1 \( \mu \)mol/L). This concentration blocked 1 to 3 nmol/L ET-1–induced constriction without altering constriction induced by 40 mmol/L KCl. The potentiating effect was suppressed by the specific protein kinase C inhibitor chelerythrine (1 \( \mu \)mol/L).

Conclusions—Ox-LDL enhances myogenic tone through the release of ET-1 from the endothelium of the rabbit posterior cerebral artery. (Stroke. 1999;30:2423-2430.)

Key Words: cerebral arteries • endothelins • lipoproteins, LDL • myogenic tone • rabbits

Low-density lipoprotein (LDL) and its oxidized form (Ox-LDL) play a crucial role in the development of atherosclerosis and related cardiovascular diseases.1,2 Ox-LDL has been detected in atherosclerotic lesions of human and rabbits.3 LDL may be oxidatively modified when incubated in vitro with endothelial and smooth muscle cells and macrophages.4–6 Isolated segments of blood vessels from animals and humans with hypercholesterolemia or atherosclerosis exhibit altered vasomotor properties similar to those produced by Ox-LDL in vitro; ie, an increase in agonist-induced contraction and inhibition of endothelium-dependent relaxation.7–9

The cerebral circulation has the intrinsic ability to maintain a relatively constant blood flow despite changes in blood pressure; ie, it autoregulates. Many factors contribute to this: constrictor and dilator neural, pressure-induced constriction, flow-dependent dilatation, and tissue metabolic products are considered the most important.10–12 Cerebral resistance arteries of both animals and humans develop myogenic tone, and this is generally considered to be the main source of their intrinsic tone.13 Although the effects of Ox-LDL on several features of vascular endothelial and smooth muscle function and their underlying mechanisms have been extensively investigated, the influence of Ox-LDL on myogenic activity of cerebral arteries has not been studied.

The objectives of the present study were to investigate whether Ox-LDL, in a concentration of pathophysiological relevance to man,9 influences myogenic activity in the rabbit cerebral artery and, if so, the mechanisms of its effect. We studied the influence of Ox-LDL on the myogenic tone developed by the rabbit posterior cerebral artery (PCA) during perfusion over the pressure range 40 to 90 mm Hg. We compared the effects of intraluminal and extraluminal exposure to Ox-LDL, because Ox-LDL uptake by its endothelial receptor may contribute to endothelial activation and dysfunction and under disease conditions, Ox-LDL can accumulate in the subendothelial space over a long period.14,15 Our results show that exposure of the artery wall on either side to

Received March 3, 1998; final revision August 5, 1999; accepted August 17, 1999.

From the Totman Laboratory for Cerebrovascular Research, Department of Pharmacology, College of Medicine, University of Vermont, Burlington. Correspondence to: Dr John A. Bevan, Totman Laboratory for Cerebrovascular Research, Department of Pharmacology, Given Bldg, College of Medicine, University of Vermont, Burlington, VT 05405-0068.

© 1999 American Heart Association, Inc.

Stroke is available at http://www.strokeaha.org
Ox-LDL (10 μg/mL) greatly enhanced myogenic tone and that this effect was inhibited by endothelium removal. The nitric oxide (NO) synthase inhibitor Nω-nitro-L-arginine methyl ester (L-NAME) failed to influence this effect. However, the specific endothelin-1 (ET-1) receptor antagonist BQ-123 and the specific protein kinase C (PKC) inhibitor chelerythrine reversed the potentiation of myogenic tone by Ox-LDL. We conclude that Ox-LDL enhances the myogenic tone of PCA through the release of ET-1 and that this involves the activation of PKC.

Subjects and Methods

Isolation of Human LDL
Plasma was separated from healthy, normolipidemic, freshly drawn human blood by centrifugation. LDL was prepared from this by sequential density gradient ultracentrifugation with density adjustment by KBr (density, 1.019 to 1.063 g/mL).16 The isolated LDL was dialyzed for 40 to 44 hours against phosphate-buffered saline to remove EDTA. Native LDL (200 μg protein per milliliter) was then stored at 4°C in the dark and used within 2 weeks. Oxidation of LDL was achieved by incubation of native LDL at a concentration of 200 μg/mL with 4 μmol/L CuCl2 overnight at room temperature.

General Preparations
Study procedures were in accordance with institutional guidelines. Thirty-five male rabbits (New Zealand White; weight, 2 to 3 kg; obtained from Myrtes Rabbitry, Thompson Station, Tenn) were anesthetized with sodium pentobarbital (40 mg/kg IV) and heparinized (1000 U/kg of heparin IV). Rabbits were killed by exsanguination, and the brain was rapidly removed and placed in ice-cold PSS, composed of the following (in mmol/L): NaCl 119, KCl 4.7, CaCl2 1.6, MgSO4 1.2, KH2PO4 1.2, NaHCO3 24.9, dextrose 11.1, and EDTA 0.026; pH 7.4. The PCA was isolated immediately.

Measurement of Vascular Diameter By Use of a Pressure-Perfusion Myograph

Segments of the rabbit PCA (2 mm in length, 250±20 μm in diameter) were placed in a microvascular chamber containing PSS aerated with 95% O2/5% CO2 (pH=7.4) at room temperature, according to the technique of Halpern and Osol.17 The segment was first mounted on the outflow microcannula and secured using single strands of surgical braided nylon suture. After pressure was raised to 5 to 10 mm Hg to flush and clear the blood from inside the vessel, the segment was mounted on the inflow microcannula, and pressure was raised to 20 mm Hg with the pressure servo-unit to check a potential leak. The blood vessel was imaged using a videocamera and a dimension analyzer (Living Systems Instrumentation) linked to a chart recorder (model 1242, Soltect). Vessels were equilibrated at 60 mm Hg at 37°C for 1 to 2 hours until myogenic tone development reached equilibrium. Acetylcholine (ACh; 3 μmol/L) was then given to test endothelial function. Diameters achieved to transmural pressures of 40, 60, 75, and 90 mm Hg were measured. At the end of each experiment, the diameter of maximum constriction on exposure to 120 mmol/L KCl and that after placement in Ca2+-free medium with EGTA (2 mmol/L) at each level of pressure used in the earlier part of the experiment were determined. Myogenic tone is defined as the percentage of the difference between maximal active and passive diameters at a given pressure.

Endothelial-cell removal was achieved in some instances by rubbing the lumen with a roughened micropipette but in most cases by a combination of rubbing and intraluminal flow. Successful removal of the endothelium was confirmed by the loss of dilation to ACh (3 μmol/L).

Experimental Protocols

Effect of Ox-LDL
The myogenic tone developed at pressures of 40, 60, 75, and 90 mm Hg was examined before and after intraluminal and extraluminal administration of Ox-LDL (10 μg/mL).3-8 This was infused into the lumen of the mounted segment by a Harvard syringe infusion pump (model 22) at a rate of 25 μL/min for 20 minutes. The extraluminal effect of Ox-LDL was examined by directly adding Ox-LDL (10 μg/mL) into the vessel chamber and incubating for 30 minutes. The effects of Ox-LDL on contractile responses to norepinephrine (NE) 0.5 to 1 μmol/L and KCl 20 mmol/L were also compared. Native LDL (100 μg/mL) was studied in a similar manner.

Cellular Mechanisms

1. The effect of Ox-LDL was examined in the presence and absence of endothelium and before and after pretreatment with the NO synthase inhibitor L-NAME (50 μmol/L). Responses to NE and KCl were tested before and after endothelium removal to determine whether the removal procedure had damaged the smooth muscle cells.

2. The effect of Ox-LDL on myogenic tone was studied in the presence and absence of the specific ET-1 antagonist BQ-123 (1 μmol/L for 1 hour). The vasoconstrictor responses to ET-1 (1 to 3 nmol/L) and KCl (40 mmol/L) were also compared in the absence and presence of the same concentration of BQ-123.

3. The effect of Ox-LDL on myogenic tone was compared in the presence and absence of the specific PKC inhibitor chelerythrine (1 μmol/L for 30 minutes).18

4. Lysophosphatidylcholine (LysoPC; 10 μmol/L) was administered in the same way as Ox-LDL. LysoPC generated during the oxidative modification of LDL is considered the main factor responsible for the inhibition of endothelium-dependent relaxation by Ox-LDL.20

Effects of Ox-LDL and LysoPC on ACh-Induced Endothelium-Dependent Vasodilation

ACh-induced dilation was compared before and after pretreatment with either Ox-LDL (10 μg/mL) or LysoPC (10 μmol/L) in intact vessels.

Drugs
ACh, BQ-123, ET-1, L-NAME, LysoPC, and NE were dissolved either in double-distilled water or in fresh PSS. Chelerythrine was dissolved in ethanol. Raised K+ (≥20 mmol/L) was prepared by substituting an equimolar amount of KCl for NaCl in the PSS.

Data Analysis

All data are presented as mean±SE, and n indicates the number of experiments performed. ACh-induced dilation was expressed as a percentage of the maximum passive diameter change measured after exposure to Ca2+-free PSS with EGTA (2 mmol/L). Data were analyzed by the paired Student t test for single comparisons and by ANOVA followed by contrast test for multiple comparisons. Differences were considered significant when P<0.05.

Results

General Characteristics
Approximately 95% of the rabbit PCA segments developed spontaneous tone within 1 to 2 hours at 60 mm Hg intramural pressure and 37°C. Under these conditions, the fully relaxed and distended diameter (ie, in Ca2+-free medium with 2 mmol/L EGTA) averaged 379.8±10.9 μm. When active tone developed, the lumen diameter was reduced by 29.5±1.8% to 263.0±9.3 μm (n=30). The segments that did not develop myogenic tone were discarded. The arteries constricted to 120 mmol/L KCl, with a mean diameter of 82.9±13.6 μm (n=10).
Effect of Ox-LDL

Intraluminal Ox-LDL
Perfusion of Ox-LDL (10 μg/mL) into the lumen of the vessel caused constriction within 5 minutes. The time course of the diameter change, particularly during the initial 10 minutes, varied, showing both a reduction of 60±15 μm and an increase of 18±2 μm in diameter. After these initial changes, the tone increase stabilized at a higher level and lasted as long as it was followed: 1 to 2 hours (P<0.001; Figure 1A).

Extraluminal Ox-LDL
When exposed extraluminally to Ox-LDL (10 μg/mL), the artery segment constricted, with a mean change in diameter from 271.5±7.4 to 213.5±4.9 μm (before versus after Ox-LDL, respectively; n=15; P<0.05). This mostly occurred during the first 5 to 10 minutes and was maintained for several hours. Diameters at pressures of 75 and 90 mm Hg also increased significantly (P<0.01; Figure 1B).

Intraluminal and Extraluminal Ox-LDL
Administration of Ox-LDL (10 μg/mL) to both intraluminal and extraluminal surfaces simultaneously did not enhance the mean level of diameter decrease to pressures between 60 to 90 mm Hg.

Effect of Ox-LDL on Responses to NE and KCl
Administration of NE (0.5 to 1 μmol/L) and KCl (20 mmol/L) caused further diameter reduction of the myogenically contracted artery of 21.4±3.1 and 48.4±7.2 μm, respectively. Although myogenic tone increased after Ox-LDL (10 μg/mL), the magnitude of the constrictions to NE and KCl were the same: NE, 21.7±5.0 μm, and KCl, 40.0±4.0 μm (n=5; P>0.05 compared with responses before Ox-LDL).

Effect of Native LDL
Native LDL (100 μg/mL) had no influence on myogenic tone. Before and after incubation with native LDL, the diameters of the arteries were 253.5±32.89 versus 258.7±35.3 μm, 238.25±34.3 versus 273.2±38.4 μm, 253.3±35.5 versus 276.2±38.4 μm, and 262.5±38.5 versus 278.5±37.0 μm at pressures of 40, 60, 75, and 90 mm Hg, respectively.

Cellular Mechanisms

Role of the Endothelium
Ox-LDL (10 μg/mL) had no effect on arterial diameter after the removal of endothelium (Figure 2A) nor was it changed after exposure to the NO synthase inhibitor L-NAME. L-NAME did not modify the potentiating effect of Ox-LDL on myogenic tone (Figure 2B). Removal of the endothelium abolished 3-mol/L ACh–induced dilation but had no influence on the constrictions to NE (0.5 to 1 μmol/L) and KCl (20 mmol/L).

Role of ET-1
ET-1 is a potent vasoconstrictor released from endothelial cells. The selective ET\(\text{A}\) receptor antagonist BQ-123 (1 μmol/L) prevented the constrictor effect of Ox-LDL (Figure 2C; P<0.01). No statistical difference occurred between the diameters of the control and treated groups (Figure 2C; P>0.05). BQ-123 (1 μmol/L) effectively antagonized ET-1 (1 to 3 nmol/L)–induced vasoconstriction (diameter change, 70.4±9.4 and 7.7±2.0 μm before and after BQ-123, respectively; P<0.001; Figure 3), but had no effect on that to KCl (40 mmol/L). The diameter decrease was 63.8±8.8 and 61.40±13.6 μm before and after BQ-123, P>0.05 (Figure 3).

Involvement of PKC
The effect of Ox-LDL on myogenic tone was suppressed by the specific PKC inhibitor chelerythrine (1 μmol/L; P<0.01; Figure 2D). At 60 mm Hg, 30-minute incubation with chelerythrine (1 μmol/L) antagonized 19.7±5.0% of the spontaneous tone; the mean diameter was 252.8±15.3 μm. Chel-
erythrine almost reversed Ox-LDL induced tone. Diameter increased from 212.3 $\pm$ 13.6 to 249.8 $\pm$ 11.4 $\mu$m.

Effect of LysoPC
Both intraluminal (10 $\mu$mol/L) and extraluminal (10 $\mu$mol/L) LysoPC significantly increased myogenic tone. The effect of LysoPC was equivalent to that of Ox-LDL at pressures between 60 to 90 mm Hg, but it was greater at a pressure of 40 mm Hg, regardless of the manner of perfusion ($P$, 0.001; Figures 4A and B). A further increase in concentration of LysoPC did not result in a further potentiating effect (data not shown).

Effects of Ox-LDL and LysoPC on ACh-Induced Dilation
ACh (0.1 to 3 $\mu$mol/L) caused concentration-dependent dilation in endothelium-intact arteries. Ox-LDL (10 $\mu$g/mL) reduced the dilation with 3 $\mu$mol/L ACh to 69.5 $\pm$ 6.7% compared with control (96.4 $\pm$ 2.2% of maximum passive diameter; $P$, 0.05; Figure 5A). LysoPC (10 $\mu$mol/L) caused a greater inhibition of the same dilation (95.8 $\pm$ 3.9% and 41 $\pm$ 3.0% of maximum passive diameter before and after LysoPC, respectively; $P$, 0.05; Figure 5B).

Discussion
The major finding in this study is that Ox-LDL at a concentration equivalent to that encountered in vivo (10 $\mu$g/mL), significantly enhanced pressure-induced myogenic tone in the rabbit PCA. This effect appears to be due to the release of ET-1 from the endothelium, a process dependent on the activation of PKC. Ox-LDL can exert its effect from either the luminal or abluminal side of the vessel. We also found that LysoPC, a lipid component of Ox-LDL, had an equivalent effect. Ox-LDL did not influence a comparable constriction to NE or KCl.

The potentiating effect of Ox-LDL on myogenic tone was substantial; the tone elevation was 21.4 $\pm$ 6.1% and 28.5 $\pm$ 1.8% at 60 and 90 mm Hg, respectively ($P$, 0.05). Given that the effect was abolished after endothelium removal but not modified by the NO synthase inhibitor L-NAME (50 $\mu$mol/L), it originates from the endothelium but is not due to inhibition of tonic release of the dilator NO. This effect was prevented by the selective ET-1A receptor antagonist BQ-123 (1 $\mu$mol/L). This concentration of BQ-123 was selected because it did not change the control tone level but almost completely antagonized the constriction to 1 to 3 nmol/L ET-1 without altering the response to 40 mmol/L KCl. BQ123 did not influence myogenic tone in the absence of Ox-LDL but influenced only the enhancement of this stretch-induced response caused by the lipid. Macarthur et al\textsuperscript{21} determined, using bovine aortic endothelial cells, that stretch caused a rapid release of the peptide. Their analysis suggests that ET-1 is released from preformed stores that are

Figure 2. Effect of Ox-LDL (10 $\mu$g/mL) on myogenic tone in rabbit PCA in endothelium-denuded vessels before (A; $n$, 7) and after 50 $\mu$mol/L L-NAME (B; $n$, 5), 1 $\mu$mol/L BQ-123 (C; $n$, 8), and 1 $\mu$mol/L chelerythrine (D; $n$, 5). Each point represents mean $\pm$ SE. *$P$, 0.05, **$P$, 0.01.
replenished by synthesis. Thus, our data suggest that the constrictor effect of Ox-LDL is mediated by the release of ET-1 from the endothelial cells of the stretched vessel wall. These results with intact vessels are in agreement with those observed from the cultured cells. Ox-LDL enhances ET secretion from human and porcine aortic endothelial cells and mesangial cells.22–24 Several other substances can both increase and decrease, some rapidly and some slowly, the release of ET-1 from cerebrovascular endothelium.25,26

High transmural pressure can cause LDL accumulation in the inner media of the vessel wall,27,28 and extraluminal lipid would be expected to readily enter the media. Our findings are consistent with this, because Ox-LDL shows a pressure-related potentiation that is independent of the arterial surface exposed. Pressure and stretch release ET-1 from human atherosclerotic coronary arteries in vivo,29 cultured human endothelial cells,30 and bovine aortic endothelial cells.31 In contrast, high pressure inhibits basal NO release.30 Consequently, Ox-LDL–induced ET-1 release from the cultured endothelial cells is not modified by exogenous NO.21 Because NO is not involved in pressure- or Ox-LDL–induced ET-1 release,21,30 it is to be expected that NO inhibition had no effect on Ox-LDL–enhanced myogenic tone of the pressurized arteries. Taken together, the sensitivity of myogenic tone to a low concentration of Ox-LDL can alternatively be explained as the result of the synergistic consequence of pressure- and Ox-LDL–induced ET-1 release from the endothelial cells.

Because the specific PKC inhibitor chelerythrine (1 μmol/L) prevented the potentiating effect of Ox-LDL on myogenic tone, PKC activation may be involved. Either basal or Ox-LDL–stimulated ET-1 release involves the activation of endothelial PKC.21 Furthermore, PKC activation is associated with ET-1 release by agonists and shear stress.32–34 Stretch-induced tone is also PKC dependent.35,36 Both Ox-LDL and pressure could act together to release ET-1 and further activate smooth muscle PKC.

The effective concentration of Ox-LDL (10 μg/mL) in this study is within the range of levels reported in humans.9,18,24 These levels of Ox-LDL and LysoPC also significantly inhibited ACh-induced endothelium-dependent dilation in the rabbit PCA. Impairment of endothelium-dependent vasodilation by these lipids has been found in large-conduit arteries,20,37,38 coronary microvessels,39 and cerebral arteries.40,41 This is probably not an effect specific to endothelium-dependent dilation.42 Although Ox-LDL has been reported to potentiate agonist-induced vasoconstrictions,43 it failed to modify the constriction responses to NE (0.5 to 1 μmol/L) and KCl (20 mmol/L) in the present study. This may be

Figure 3. Constrictor responses in rabbit PCA to 1 to 3 nmol/L ET-1 (n=7) and 40 mmol/L KCl (n=5) before and after pretreatment with the ET₄ receptor antagonist BQ-123 (1 μmol/L). Each point represents mean±SE. ***P<0.001.

Figure 4. Effect of LysoPC (10 μmol/L) administered intraluminally (A) and extraluminally (B) on myogenic tone in rabbit PCA developed between 40 and 90 mm Hg. Each point represents mean±SE; n=7. ***P<0.001.
because these dosages of NE and KCl do not significantly activate PKC.

Our observations support the conclusion that the effect of Ox-LDL in the present study is due to its oxidized form. First, native LDL had little influence on myogenic tone. Although the role of native LDL in the regulation of vascular tone is inconsiderable,38,44 studies have noted that at a higher concentration it has the potential to impair vascular function.39,45 Second, LysoPC generated during the oxidative modification of LDL5 had a potentiating effect equivalent to that of Ox-LDL, which suggests that LysoPC is the essential augmenting element.

LDL has been reported to enter the aortic wall in vivo through both luminal and adventitial sides.46 However, whether the cellular responses evoked by exposure of Ox-LDL to the luminal and abluminal surfaces of the cells are the same is unknown. Our results revealed that Ox-LDL, given either intraluminally or extraluminally, had the same potentiating effect on myogenic tone and that its effect is not greater when simultaneously given through both surfaces. This suggests that the effect of Ox-LDL is completely independent of its surface of entry.

Cerebral blood flow and its autoregulation are mainly controlled by the integration of neural, intraluminal pressure, endothelium-dependent shear stress, and metabolic processes. However, augmentation of the myogenic response would tend to decrease cerebral blood flow and increase the gradient of pressure fall along the cerebrovascular tree. Exactly how effectively the other regulating factors compensate for this action is not known. A decrease in cerebral blood flow would tend to diminish flow-induced vasodilation, probably to enhance the resistance increase associated with sympathetic vasoconstrictor activity, and to lead to the accumulation of metabolites. Thus, it is reasonable to conclude that the action of Ox-LDL on myogenic tone studied in the present article would result in the attenuation of cerebral flow and diminish its effective regulation.

Acknowledgments

This study was supported by a grant from the Totman Laboratory for Cerebrovascular Research. We wish to thank Drs Rosemary Bevan, Marlene Cohen, and Eric Thorin for helpful suggestions and discussions during this study; Alan Harward for assistance with the statistical analysis; and Pat Englert for expert secretarial assistance.

References

Low-density lipoprotein (LDL) has been shown to impair agonist-induced nitric oxide synthase–dependent relaxation of peripheral blood vessels.1,2 In addition, vascular dysfunction during disease states has been attributed to elevated LDL levels.3–5 The mechanism by which LDL impairs nitric oxide synthase–dependent vasorelaxation is not entirely clear but may involve the formation of oxygen radicals to inactive nitric oxide, a direct effect on nitric oxide production, a direct effect on G proteins, or stimulation of vasoactive products to modulate the effects of nitric oxide on blood vessels.6,7

Cerebral blood flow remains relatively constant during changes in arterial pressure because of the ability of cerebral resistance vessels to develop myogenic tone. Because LDL appears to affect various aspects of endothelial cell and vascular smooth muscle cell function, the authors of the present study were interested in examining the effect of LDL on myogenic activity of cerebral arteries. The authors examined the effect of oxidized LDL (Ox-LDL) on myogenic tone of the rabbit posterior cerebral artery. They report that Ox-LDL significantly enhanced myogenic tone but did not alter constriction of cerebral arteries in response to norepinephrine or potassium chloride. They report that Ox-LDL significantly enhanced myogenic tone but did not alter constriction of cerebral arteries in response to norepinephrine or potassium chloride. They report that Ox-LDL significantly enhanced myogenic tone but did not alter constriction of cerebral arteries in response to norepinephrine or potassium chloride.
is elevated. Presumably, an accumulation of LDL in the vascular wall would impair nitric oxide synthase–mediated cerebral vasodilation and enhance myogenic cerebral vasoconstriction, which could lead to a decrease in cerebral blood flow.

William G. Mayhan, PhD, Guest Editor
Department of Physiology and Biophysics
University of Nebraska Medical Center
Omaha, Nebraska

References
Oxidized Low-Density Lipoprotein Enhances Myogenic Tone in the Rabbit Posterior Cerebral Artery Through the Release of Endothelin-1
Hui Xie and John A. Bevan

Stroke. 1999;30:2423-2430
doi: 10.1161/01.STR.30.11.2423

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/30/11/2423