Effects of Cocaine on Carotid Vascular Reactivity in Swine After Balloon Vascular Injury

Boris D. Núñez, MD; Lin Miao, MD, PhD; James N. Ross, DVM, PhD; Mireya M. Núñez, MD; Donald S. Baim, MD; Joseph P. Carrozza, Jr, MD; James P. Morgan, MD, PhD

Background and Purpose The use of cocaine has been associated with stroke. To evaluate carotid vasospasm as a potential mechanism of cocaine-induced stroke, we studied 12 swine immediately and 10 weeks after angioplasty.

Methods We compared the short- and long-term vasoconstrictor responses of normal and injured arterial segments to nitroglycerin, histamine, and cocaine in vivo by carotid angiography. We also compared the isometric contractile force responses to different vasoactive substances in normal and injured vascular rings in vivo, and we tested the direct action of cocaine on both arterial segments.

Results In in vivo studies, immediately after angioplasty, luminal diameter in the control segment decreased by 30% with histamine 30 μg/kg and by 23% with cocaine 10 mg/kg (P<.001). In contrast, neither histamine nor cocaine produced vasoconstriction in the angioplasty segment. Thus, a transient loss of vasoconstriction occurred at the angioplasty site. Ten weeks later, histamine 30 μg/kg significantly (P<.001) decreased luminal diameter by 34% in the control and by 33% in the angioplasty segment; similarly, cocaine 10 mg/kg significantly (P<.001) decreased luminal diameter by 26% in the control and by 34% in the angioplasty segment. Thus, 10 weeks after angioplasty, the transitory loss of carotid vasoconstriction in response to histamine and cocaine reverted, and a moderate generalized vasoconstriction occurred in both segments without localized vasoconstriction. In vitro, the maximal isometric tension responses to KCI, acetylcholine, histamine, and phenylephrine were similar in vascular rings from normal and angioplasty segments. The median effective doses to histamine and phenylephrine were similar. In contrast, cocaine in concentrations from 10^-7 to 10^-3 mol/L failed to produce any isometric contraction in vitro.

Conclusions Cocaine in vivo produced a generalized carotid vasoconstriction without evidence of localized vasoconstriction; since there was no response to cocaine in vitro, the in vivo effect was most likely mediated by neurohumoral factors rather than by a direct action of cocaine on vascular smooth muscle. (Stroke. 1994;25:631-638.)

Key Words • angioplasty • carotid arteries • cocaine • vasoconstriction

Cocaine abuse is a major social and medical problem and has become a significant cause of stroke, especially in young adults.1-3 Recent studies show a strong temporal association of the use of cocaine with ischemic and hemorrhagic cerebrovascular accidents.4-7,14 Cocaine-related strokes can occur in normal or abnormal cerebral vessels,6,11 but patients with underlying berry aneurysms and arteriovenous malformations may be at particular risk of cerebral hemorrhage after the use of cocaine.15 Although normal vessels were found in approximately half of the patients, several angiographic studies in patients with cocaine-associated cerebral infarction have demonstrated the following vascular abnormalities: (1) single or multiple intracranial large-vessel stenoses or occlusions, (2) occlusion of the extracranial internal carotid artery, (3) carotid vasospasm, and (4) intraluminal thrombosis in the internal carotid artery.4,7,9,11,15-17 Moreover, Flores et al16 have demonstrated cocaine-induced vasoconstriction in both diseased and nondiseased coronary artery segments but found a marked vasoconstriction in the segments with advanced atherosclerosis. Thus, possible mechanisms of cocaine-related stroke may include (1) localized carotid vasospasm, (2) enhanced platelet aggregation, (3) vasculitis, and (4) sudden rise in arterial blood pressure with possible direct cerebral vasoconstriction due to adrenergic stimulation. We tested the hypothesis that cocaine can induce carotid artery vasospasm. We used the swine model of vascular injury to evaluate the short- and long-term effects of histamine and cocaine on carotid vascular reactivity after balloon vascular injury. This model has been useful for studying the complex processes of neointimal proliferation, thrombosis, elastic recoil, and vasospasm.19

Our specific aims were (1) to compare the short- and long-term vasoconstrictor responses of normal and injured arterial segments to nitroglycerin, histamine, and cocaine in vivo by carotid angiography and (2) to compare the isometric contractile force responses to different vasoactive substances in normal and injured

See Editorial Comment, page 638
vascular rings in vitro, as well as to test the direct action of cocaine on both arterial segments.

Materials and Methods

Twelve Yorkshire swine (Tufts University School of Veterinary Medicine, breeding laboratories) aged 3 to 4 months and weighing 30 to 40 kg were sedated with intramuscular ketamine hydrochloride (12.5 mg/kg, Quad Pharmaceutical, Inc) and diazepam (10 mg, Roche Laboratories Inc). All animals were intubated and mechanically ventilated (Harvard respirator, Harvard Apparatus). Anesthesia was maintained with a mixture of 1.5% to 2% isoflurane plus oxygen. Arterial pH, P02, Pco2, and temperature were kept within the normal physiological range. Heparin (5000 U) was given intravenously by a bolus injection, and normal saline solution (50 mL/h) and heparin (5000 U bolus) were continuously infused through a cannula inserted into an ear vein during the experiment. A right femoral cutdown was performed, and the femoral artery was exposed and then cannulated with a 10F sheath. An 8F right Judkins catheter (Medtronic Interventional Vascular Inc) was advanced from the femoral artery and engaged in the orifice of the common carotid artery. Systemic pressures were constantly monitored and recorded with a multichannel physiological recorder (Hewlett Packard Company). A bipolar chest lead II was attached to provide electrocardiographic and arrhythmia monitoring.

Carotid Angiography

Angiograms were performed in the anterior-posterior projection throughout the experiment. Cineraingiograms were performed with a General Electric angiographic unit and recorded on 35-mm cine film at a speed of 50 frames per second using nonionic contrast medium (iopamidol 76%, Squibb Diagnostico). Carotid angiography was performed under basal conditions and 5 minutes after the intravenous administration of nitroglycerin (0.4 mg). Values of vessel diameter after the administration of nitroglycerin were used as standards to calculate percent change of these variables. The measurement of carotid artery diameter was performed by digital caliper (Fowler-Ultra-Cal II). Two carotid artery segments were measured in the right and left carotid, one in the proximal segment (angioplasty site) and one in the distal segment (control site), as shown in Fig 1.

Isometric Force Recording In Vitro

After completing the second angiographic study, carotid arteries were quickly removed and cleaned of the perivascular tissue. Four pairs of vascular arterial rings, 2 to 3 mm in length, were prepared from each carotid artery. Two vascular rings from the proximal segment (angioplasty site) and two vascular rings from the distal segment (control site) were mounted in organ baths filled with 50 mL of physiological salt solution gassed with 95% O2/5% CO2 at 30°C (pH 7.3 to 7.4). The composition of the physiological salt solution was (mmol/L) NaCl 120, KCl 5.9, dextrose 11.5, NaHCO3 25, MgCl2 1.2, NaH 2PO4 1.2, and CaCl2 2.5. The 60-mmol/L KCl solution was made by replacing equimolar NaCl with KCl.

Drugs and Chemicals

Histamine hydrochloride, L-phenylephrine hydrochloride, and acetylcholine chloride were obtained from Sigma Chemical Company. Cocaine hydrochloride was obtained from the National Institute on Drug Abuse. Nitroglycerin was obtained from Warner-Lambert Company. Cefazolin was obtained from Baxter Healthcare Corporation.

Angioplasty Technique

Through the 10F femoral arterial sheath, an 8F balloon dilatation catheter (Meditech polyethylene balloon; size, 8 mm in diameter by 3 cm in length) was advanced under fluoroscopic guidance to the left common carotid artery for arterial dilatation. Balloon angioplasty was first performed in the proximal segment of left carotid artery and then in the
angiography was performed at 2 to 4 minutes after the angioplasty and at 5 minutes immediately after the administration of nitroglycerin (0.4 mg IV). Thirty minutes after angioplasty, the acute histamine protocol study was performed. In protocol 1 (histamine study), baseline angiograms were performed, then histamine (10, 20, or 30 µg/kg administered intra-arterially into the common carotid artery) was given at 10-minute intervals. Angiograms were performed 1 to 2 minutes after the administration of histamine. A 60-minute washout period was allowed to elapse between the histamine and cocaine protocols. In protocol 2 (cocaine study), baseline angiograms were performed, then cocaine (1, 3, or 10 mg/kg IV) was given at 10-minute intervals. Angiograms were performed 2 to 4 minutes after the administration of cocaine. After the completion of the study, the right femoral artery was ligated with 2.0 silk and the skin incision closed with a running subcuticular 3.0 vicryl suture. Cefazolin 1 g was given intravenously. After confirming that the animals had recovered from surgery and anesthesia, they were housed in a temperature-controlled animal ward (New England Veterinary Medical Center, North Grafton, Mass) and fed a regular chow diet. The animals were carefully evaluated and followed for any sign of stroke, fever, or change in behavior.

**Chronic Study**

In the in vivo study, 10 weeks after the initial angioplasty procedure a baseline angiogram was obtained; then the animals were rechallenged, first with histamine and then with cocaine as previously described. In the vascular ring segments from the angioplasty site and the control site, the following in vitro studies were performed: (1) response to 60 mmol/L KCl; (2) dose-response curve to histamine (10⁻⁸ to 10⁻³ mol/L); (3) dose-response curve to acetylcholine (10⁻⁸ to 10⁻⁶ mol/L); (4) dose-response curve to phenylephrine (10⁻⁸ to 10⁻⁵ mol/L); and (5) dose-response curve to cocaine (10⁻⁷ to 10⁻⁵ mol/L). The contractile responses were expressed as percent change of the response produced by 60 mmol/L KCl.

**Statistical Analysis**

Data were expressed as mean±SEM. Carotid artery segments before and after each drug intervention (ie, histamine or cocaine) were compared using ANOVA for repeated measures. When a significant difference was detected, multiple comparison analysis was performed using Scheffe’s and Fisher’s tests. A value of P<.05 was considered statistically significant. Student’s t test was used to compare the histological findings of the control with angioplasty segments and to compare the contractile response (isometric force) or pD₂ [−log(ED₅₀)] between the rings from control or angioplasty segments.

**Results**

**Body Weight and Carotid Diameter**

Initial body weight increased significantly from 25±0.5 to 31±0.8 kg (P<.05) after 10 weeks. In contrast, no significant difference in luminal diameter was observed.

**Experimental Protocols**

The short- and long-term protocols are outlined in Fig 2.

**Acute Study**

After baseline carotid angiograms, bilateral carotid balloon angioplasty was performed as previously described. Carotid angiography was performed at 2 to 4 minutes after the angioplasty and at 5 minutes immediately after the administration of nitroglycerin. Thirty minutes after angioplasty, the acute histamine protocol study was performed. In protocol 1 (histamine study), baseline angiograms were performed, then histamine (10, 20, or 30 µg/kg administered intra-arterially into the common carotid artery) was given at 10-minute intervals. Angiograms were performed 1 to 2 minutes after the administration of histamine. A 60-minute washout period was allowed to elapse between the histamine and cocaine protocols. In protocol 2 (cocaine study), baseline angiograms were performed, then cocaine (1, 3, or 10 mg/kg IV) was given at 10-minute intervals. Angiograms were performed 2 to 4 minutes after the administration of cocaine. After the completion of the study, the right femoral artery was ligated with 2.0 silk and the skin incision closed with a running subcuticular 3.0 vicryl suture. Cefazolin 1 g was given intravenously. After confirming that the animals had recovered from surgery and anesthesia, they were housed in a temperature-controlled animal ward (New England Veterinary Medical Center, North Grafton, Mass) and fed a regular chow diet. The animals were carefully evaluated and followed for any sign of stroke, fever, or change in behavior.

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**Results**

**Body Weight and Carotid Diameter**

Initial body weight increased significantly from 25±0.5 to 31±0.8 kg (P<.05) after 10 weeks. In contrast, no significant difference in luminal diameter was observed.
Thirty minutes after balloon angioplasty, the carotid lumen diameters in response to histamine appeared to decrease with each dose in the control segment, reaching statistical significance with the 30-μg/kg dose. In contrast, carotid lumen diameters did not change in the angioplasty segment. Thus, histamine induced generalized vasoconstriction in the control segment but not in the acutely angioplastied segment, reflecting a transient loss of carotid vasoconstriction. However, 10 weeks after angioplasty the carotid lumen diameters appeared to decrease in the control and angioplasty segments, reaching statistical significance with the 30-μg/kg dose. Also, a similar degree of vasoconstriction occurred in both segments; the angioplasty segments decreased in luminal diameter by 66% and the control segments by 65%. Thus, 10 weeks after angioplasty the transient loss of vasoconstriction in the angioplasty segment reversed, and histamine produced a generalized vasoconstriction without evidence of localized vasospasm.

**Short- and Long-term Vasomotor Reactivity to Cocaine In Vivo**

Thirty minutes after balloon angioplasty, the carotid lumen diameters appeared to decrease with each dose in the control segment, reaching statistical significance with the 10-mg/kg dose (Table 2). In contrast, the carotid lumen diameters in the angioplasty segment did not change. Thus, cocaine induced generalized vasoconstriction in the normal but not in the acutely angioplastied segment, reflecting a transient loss of carotid vasoconstriction. However, 10 weeks after angioplasty, the carotid lumen diameters of the control and angioplasty segments decreased with each cocaine dose and reached statistical significance with the 10-mg/kg dose (Figs 4 and 5). Also, a similar degree of vasoconstriction was observed in both segments; the control segment decreased in luminal diameter by 75% and the angioplasty segment by 65%. Thus, 10 weeks after angioplasty the transitory loss of vasoconstriction in the angioplasty segment was completely reversed in the angioplasty segment, and cocaine induced generalized vasoconstriction in both segments, without evidence of localized vasospasm.

**Table 2. Short- and Long-term Effects of Histamine and Cocaine on Carotid Artery Diameter In Swine After Angioplasty**

<table>
<thead>
<tr>
<th>Time After Angioplasty</th>
<th>Histamine Doses, μg/kg</th>
<th>Cocaine Doses, mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>5</td>
</tr>
<tr>
<td>30 Minutes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control segment (n=12)</td>
<td>4.8±0.7</td>
<td>4.6±0.7</td>
</tr>
<tr>
<td>Angioplasty segment (n=12)</td>
<td>5.2±0.9</td>
<td>4.8±0.9</td>
</tr>
<tr>
<td>10 Weeks</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control segment (n=24)</td>
<td>4.1±0.2</td>
<td>3.8±0.2</td>
</tr>
<tr>
<td>Angioplasty segment (n=24)</td>
<td>4.2±0.2</td>
<td>3.8±0.1</td>
</tr>
</tbody>
</table>

Values are diameters (in millimeters), expressed as mean±SEM.

*P<.05, †P<.001 different from baseline.
Responses of Vascular Ring Segments to Vasoactive Agents In Vitro

There were no statistical differences in the resting force ($0.78 \pm 0.1$ versus $0.74 \pm 1$, $10^3 \times N/m^2$) or active contraction evoked by $60 \text{ mmol/L KCl}$ solution ($0.11 \pm 0.9$ versus $0.10 \pm 0.1$, $10^3 \times N/m^2$) in the vascular rings isolated from the control or the angioplasty segments. During increasing concentration of histamine, the maximal tension ($5.1 \pm 0.2$ versus $5.1 \pm 0.1$, $10^3 \times N/m^2$) of the control segment and that of the angioplasty segment were similar. In addition, the dose-response curve to histamine was not different in the two segments. Phenylephrine evoked a similar degree of contraction ($0.7 \pm 0.1$ versus $0.6 \pm 0.2$, $10^3 \times N/m^2$), and the $ED_50$ values in control and angioplasty segments were similar ($5.4 \pm 0.3$ versus $5.3 \pm 0.2$, $10^3 \times N/m^2$). Furthermore, acetylcholine produced a vigorous contraction in control and angioplasty segments. In contrast, cocaine in concentrations from $10^{-7}$ to $10^{-3} \text{ mol/L}$ did not produce any active force in vascular rings of either control or angioplasty segments (Fig 6).

Histological Study

The mean intimal wall thickness was significantly increased in the angioplasty segment compared with the control segments ($99 \pm 17$ versus $12 \pm 4 \mu m$; $P<.05$); in addition, the maximal intimal wall thickness was also significantly increased in the angioplasty segments compared with the control segments ($216 \pm 42$ versus $26 \pm 11 \mu m$; $P<.05$; Fig 7).

Complications

Three swine expired after the 10-mg/kg cocaine dose with severe hypotension and ventricular tachycardia, and one swine expired after the 30-μg/kg dose of histamine with an acute myocardial infarction. Acute unilateral carotid artery occlusion occurred in three swine after the administration of cocaine. One swine developed symptoms of acute stroke, manifested as partial right hemiparesis and head tilt (Fig 4). The hemiparesis and head tilt resolved in 2 weeks. The left carotid artery specimens revealed thrombosis at the site of the angioplasty. Two other swine had carotid arteries occluded without clinical manifestation.

Discussion

The present study was designed to determine the in vivo and in vitro effects of cocaine on carotid vascular reactivity in the swine model of balloon vascular injury. The major findings in our study are as follows: (1) Cocaine in vivo produced a moderate generalized vasoconstriction without evidence of localized vasospasm. (2) In vivo, a transitory loss of cocaine- and histamine-induced vasoconstriction was observed immediately after balloon injury. This transitory loss of vasoconstriction reverted to normal at 10 weeks. (3) In vitro, cocaine in concentrations up to $3 \times 10^{-3} \text{ mol/L}$ failed to produce isometric vascular contraction in either the control or the angioplasty segments. (4) In vitro, histamine, $KCl$,
and phenylephrine produced similar degrees of isometric vascular ring contraction in both the control (normal histological section) and angioplastied segments (neointimal proliferation). (5) In vitro, 10 weeks after balloon angioplasty, all swine developed significant intimal hyperplasia in response to the balloon injury at the angioplasty site.

Cocaine is an agent that can produce marked arterial vasoconstriction and vasospasm. Immediately after balloon angioplasty, cocaine induced a moderate generalized vasoconstriction in the normal segment but not in the acutely injured segment. Similarly, lack of vasoreactivity in the acutely injured segment ("arterial paralysis") has been found with other vasoactive drugs such as ergotamine and nitroglycerin. Previous animal experiments have suggested that balloon angioplasty produces severe smooth muscle injury and arterial paralysis by severe arterial luminal stretching caused by an oversized balloon. The loss of vascular reactivity after angioplasty is a temporary phenomenon. Consigny et al. observed arterial paralysis in segments of arterial rings from rabbits immediately after angioplasty with complete reversal 28 days later, suggesting that elastic vascular recoil after angioplasty is a temporary phenomenon; similar observations have been noted by others.

Accordingly, in our study, vasomotor reactivity was regained at the angioplasty site at 10 weeks after angioplasty. Cocaine and histamine produced a generalized, uniform vasoconstriction in both the control and the angioplastied segments, without any evidence of localized vasospasm. It is possible that cocaine could cause severe vasoconstriction following other forms of vascular injury; one study demonstrated that cocaine increased coronary vascular reactivity in miniature pigs after endothelial balloon denudation.

Previous animal studies in squirrel monkeys and dogs have demonstrated that the acute administration of cocaine to conscious animals will increase the systemic pressure and heart rate. However, in anesthetized dogs the arterial pressure and heart rate response may be blunted or even decreased. Moreover, Egashira et al. showed an increase in heart rate and arterial pressures when cocaine was given to anesthetized Yucatan miniature swine. In addition, the amount of cocaine administered may determine the variable effect on heart rate and arterial pressure. In several studies low cocaine doses (from 0.0625 to 0.25 mg/kg) produced no significant change in systemic arterial pressure, whereas in others studies high cocaine doses (from 5 to 10 mg/kg) decreased systemic pressures. In our study heart rate and arterial pressure did not change after the administration of histamine. In contrast, progressive cocaine doses induced a gradual reduction in heart rate and arterial pressure, especially with the 3-mg/kg and 10-mg/kg doses. This paradoxical decrease in arterial pressure may have evoked a reflexive systemic peripheral vasoconstriction that had an impact on the carotid arteries as well. Because we only measured carotid artery segments, it is not possible for us to separate the extent to which the carotid vasoconstriction observed was related to cocaine effects or reflexive vasoconstriction.

In spite of the angiographic evidence that cocaine produced a generalized carotid vasoconstriction in the vessels in vivo, cocaine in concentrations up to $3 \times 10^{-3}$ mol/L did not produce any active contraction in the normal or abnormal (severe intimal hyperplasia) carotid artery segments in vitro. Both segments responded with similar and equal isometric vascular contraction to KCl, histamine, phenylephrine, and acetylcholine, suggesting that the functional integrity of agonist receptors on the cell was well preserved. Accordingly, similar observations have been reported in human coronary arteries from patients with end-stage heart failure and in miniature pig coronary arteries. In contrast, studies in rabbit aorta, rat tail artery, and guinea pig portal vein showed that cocaine produced contractile responses in vitro. These variable vascular effects of cocaine may depend on differences in distribution or density of adrenergic receptors and sympathetic innervation among the different species studied. Thus, from these data, it is reasonable to conclude that cocaine-induced carotid vasoconstriction in vivo occurred through a secondary release of humoral and/or neural...
vascular substances but not by a direct action of the drug on the carotid arterial smooth muscle.

Study Limitations

This study has several important limitations. Because the physiological effects of cocaine vary widely between species and with experimental conditions, these findings cannot be extrapolated directly to other species or to conscious animals. In experimental studies in humans, central euphoric effects of cocaine have been reported after intravenous doses of 1.5 mg/kg or less. 34-37 Although it is likely that some users are commonly exposed to even larger doses, 37 in some reported pathological series, cocaine concentrations in excess of 5 x 10^-5 mol/L have been found in the blood. 38,39 However, it is likely 24 that the presence of general anesthesia in our experimental animals produces a significant rightward shift in the cocaine dose-response relation (desensitization) of our animals, although this remains to be definitively tested. In addition, long-term administration in humans can result in rapid development of tolerance 38,39 that can dramatically shift the dose-response relation and increase the minimally effective concentration required to produce actions on the central nervous system and peripheral vasculature. Therefore, caution must be exercised in extrapolating quantitative cocaine doses and the expected physiological responses to humans. In addition, the cumulative dosing scheme used in our experiments may have produced slightly different results from those that would be observed after a single large dose of cocaine. However, the similarities of physiological responses of pigs and humans support the hypothesis that cocaine would produce the same effects in both species and that the effective dose in the conscious, recreational cocaine abuser may be much smaller than in the current series.

Finally, it is possible that the reduction in carotid artery diameter during infusion of the highest dose of cocaine (Table 2) may in part represent passive collapse since the arterial blood pressure had fallen substantially. However, we believe that lack of response in the angioplasty segment at this point after the procedure most likely reflects the transient effects of stretch produced by the oversized balloon used in these experiments, an effect on carotid responsiveness that would be expected to revert to normal at 10 weeks (Table 2), as has been our experience in angioplastied human coronary arteries.

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References

Administration of cocaine leads to complex cardiovascular changes and in some cases pathological sequela, including vasospasm, cardiac depression, and stroke. Effects of cocaine on individual arteries may vary according to factors such as specific organ or tissue examined, vessel size, developmental stage, level and type of anesthetic agent used, intactness and type of vascular innervation, functional status of endothelium, presence of other substances of abuse, and probably as-yet undefined conditions. Because of the prevalence of cocaine use in modern society, there is a need to understand the cardiovascular effects of this substance.

The study by Núñez et al provides interesting new data on the responsiveness of the swine carotid artery to cocaine in vivo and in vitro. In vivo, moderate carotid artery constriction following intravenous cocaine administration was abolished by the balloon injury, but normal vasoconstriction returned 10 weeks later. Vascular stretch due to the balloon injury probably led to both endothelial and smooth-muscle dysfunction. In contrast to the in vivo responses, normal carotid artery rings failed to constrict in vitro. Thus, cocaine has no direct constrictor effects on carotid artery in this preparation. The factors promoting in vivo carotid vasoconstriction are unclear but probably due in part to reflex activation of sympathetic pathways or increased levels of circulating humoral agents, such as epinephrine, due to cocaine administration. In the anesthetized dog preparation, cocaine could elicit such responses as a consequence of reduced arterial blood pressure or the central effects of cocaine. Further, it has been shown that cocaine is able to potentiate sympathetic vasoconstriction by inhibiting reuptake of norepinephrine. How ever, the exact nature of factors promoting carotid vasoconstriction by cocaine need to be elucidated.

David W. Busija, PhD, Guest Editor
Department of Physiology and Pharmacology
Bowman Gray School of Medicine
Winston-Salem, NC

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