Neuronal Excitotoxicity after Carotid Angioplasty and Stent Placement Procedures[1]

Florentino Nombela, MD, PhD
Miguel Blanco, MD, PhD
Natalia Pérez de la Ossa, MD, PhD
José Luis Caniego, MD, PhD
Tomás Sobrino, PhD
Domingo Escudero, MD, PhD
Francisco Campos, PhD[2]
María Ángeles Moro, PhD
Ignacio Lizasoaín, MD, PhD
Antoni Dávalos, MD, PhD
José Castillo, MD, PhD
José Vivancos, MD, PhD

Purpose: To investigate if glutamate levels also increase in carotid angioplasty and stent placement (CAS) procedures, since high plasma glutamate levels are associated with ischemic infarction and transient ischemic attacks, but the length of ischemia needed to elicit such elevation has not been assessed.

Materials and Methods: All patients or their relatives signed informed consent. By using high-performance liquid chromatography, plasma glutamate concentrations were determined in 74 patients treated with CAS. Blood samples were obtained with arterial and peripheral venous catheterization before and after the procedure, and venous blood samples were obtained 24, 48, and 72 hours after CAS. Glutamate concentrations were also analyzed in two different control groups: 16 patients without carotid stenosis before and after diagnostic cerebral angiography and 20 patients treated with coronary angioplasty and stent placement. The χ^2 test, *t* test, and analysis of variance were used to compare glutamate concentrations among the groups.

Results: Baseline glutamate concentrations were similar between patients who underwent CAS and both control groups. In CAS patients, glutamate concentrations in venous blood increased immediately after the procedure (354.1 μmol/L ± 132.8) and returned to baseline levels at 24 hours (129.5 μmol/L ± 56.8) ($P < .0001$). Glutamate concentrations remained unchanged over time in both control groups.

Conclusion: A rapid increase in plasma glutamate levels occurs after CAS procedures, unrelated to stroke.

[1] From the Stroke Unit, Departments of Neurology (F.N., J.V.) and Neuroradiology (J.L.C.), Hospital Universitario La Princesa, Princesa Health Research Institute, Diego de León 62, 28006 Madrid, Spain; Clinical Neurosciences Research Laboratory, Department of Neurology-Neurovascular Unit, Hospital Clínico Universitario, Universidad de Santiago de Compostela, Santiago de Compostela, Spain (M.B., T.S., F.C., J.C.); Stroke Unit, Department of Neurology, Hospital Universitari Germans Trias i Pujol, Barcelona, Spain (N.P.d.l.O., D.E., A.D.); and Neurovascular Research Unit, Department of Pharmacology, Facultad de Medicina, Universidad Complutense, Madrid, Spain (M.A.M., I.L.).
Received October 13, 2011; revision requested December 21; revision received April 2, 2012; accepted April 25; final version accepted January 17, 2013. **Address correspondence to** J.V. (e-mail: *jvivancosm@meditex.es*).

[2] **Current address:** Department of Radiology, Massachusetts General Hospital, Charlestown, Mass.

Glutamate-mediated excitotoxicity is one of the pathophysiological mechanisms of spreading brain injury in acute ischemic stroke (1,2). The overactivation of glutamate ionotropic receptors (mainly *n*-methyl-D-aspartate–NMDA) and metabotropic receptors leads to high intracellular calcium concentrations and initiates the process known as ischemic cascade. Increased levels of extracellular glutamate in acute cerebral ischemia are the result of presynaptic release and the failure of glutamate homeostatic transport system. Excitatory amino acid transporters, which usually uptake extracellular glutamate into neurons, glia, and endothelial cells, can contribute to the release of glutamate from intracellular spaces under ischemic conditions (3–5).

In clinical studies, both serum and cerebrospinal fluid levels of glutamate within the first hours of acute ischemic stroke show a high positive correlation with the extent of the infarct growth and poor functional outcome (1,6–8). Furthermore, sustained high glutamate concentrations up to 24 hours after symptom onset have been associated with early neurologic worsening, while in stable or improving ischemic stroke, glutamate levels rapidly return to baseline values (9). High plasma glutamate levels are associated with ischemic infarction and transient ischemic attacks, but the length of ischemia needed to elicit such elevation has not been assessed.

To investigate the organ-specific release of glutamate in brain ischemia and its serum profile after a short period of cerebral ischemia, we assessed glutamate serum levels in a group of patients who underwent carotid angioplasty and stent placement (CAS) and in two control groups assigned to endovascular procedures without any interruption of cerebral blood flow. The purpose of our study was to investigate if glutamate levels also increase in CAS procedures.

Advances in Knowledge

- Serum levels of glutamate elevate in carotid angioplasty and stent placement (CAS) procedures (129.7 μmol/L ± 113.0 vs 354.1 μmol/L ± 132.8), such as in patients with acute stroke.
- Glutamate levels do not change with other radiologic procedures, such as cerebral arteriography or coronary angioplasty and stent placement.
- Acute brain ischemic lesions can be found after CAS in up to 41.8% of patients examined with diffusion-weighted MR imaging before and after the procedure.
- Glutamate increase is higher in patients with acute ischemic lesions (375.3 μmol/L ± 75.5), but it is also significantly higher than baseline (129.7 μmol/L ± 113.0) in patients without acute lesions (308.1 μmol/L ± 63.3).
- Molecular changes associated with ischemia began after few seconds of brain ischemia.

Materials and Methods

This was a prospective study that included a total of 74 patients treated with CAS at two tertiary stroke centers from September 2003 until February 2007. All patients or their relatives signed informed consent according to the guidelines of the Ethics Committee of Hospital Universitario de La Princesa.

Inclusion criteria for CAS were *(a)* symptomatic patients with greater than 70% ipsilateral internal carotid artery (ICA) stenosis or greater than 60% stenosis if there was a contralateral high-degree carotid stenosis (> 70%) and *(b)* asymptomatic patients with ICA stenosis greater than 80% and ipsilateral silent brain infarcts visible on a brain scan or exhaust brain hemodynamic reserve or ICA stenosis greater than 60% if there was a contralateral carotid occlusion. Exclusion criteria were *(a)* no informed consent accepted ($n = 0$); *(b)* lack of samples needed for the study ($n = 5$); or *(c)* ischemia not confirmed with transcranial Doppler ultrasonographic (US) monitoring during CAS procedure, decrease of 50% or more in mean velocity in the side treated, or both ($n = 6$). The degree of carotid stenosis was measured according to the North American Symptomatic Carotid Endarterectomy Trial criteria (10).

The treatment group consisted of 24 (32.4%) patients who had presented with asymptomatic carotid stenosis; 23 (31.1%) patients, with ipsilateral transitory ischemic attack; and 27 (36.5%) patients, with ipsilateral ischemic stroke. The median time between transient ischemic attack or ischemic stroke and performance of CAS was 14.9 days ± 5.9 (standard deviation) (range, 6–34 days). Thirty of the 55 patients (54.5%) underwent magnetic resonance (MR) imaging after symptom onset and prior to stent placement.

The first control group consisted of 20 consecutive patients treated with coronary angioplasty and stent placement at the Coronary Unit of our center. The patients had no previous stroke and were specifically asked

Implication for Patient Care

- Glutamate may be a marker of transient brain ischemia in the setting of temporary carotid occlusion.

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Abbreviations:
CAS = carotid angioplasty and stent placement
ICA = internal carotid artery

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Conflicts of interest are listed at the end of this article.

about neurologic transient symptoms in the previous 24 hours prior to cardiac symptoms. The second control group consisted of 16 consecutive patients who underwent diagnostic cerebral angiography; there were no atheromatous lesions in supraaortic trunks. Angiography had been recommended in seven patients with intracranial arteriovenous malformations, seven patients with intracranial aneurysms, and two patients with extracranial tumors. Demographic variables, including most common vascular risk factors, were collected from all patients in the treatment and control groups.

CAS Technique

Angioplasty procedures were performed with local anesthesia by using a transfemoral approach. Patients were monitored with an electrocardiogram and noninvasive arterial blood pressure measurements. Brain blood flow was monitored in both middle cerebral arteries with transcranial Doppler US (Multi-Dop DWL; Elektronische Systeme, Sipplingen, Germany) at two depths with a 2-MHz probe through the temporal window. A decrease in flow was seen related to carotid occlusion while balloon dilation was performed. Hemodynamic complication was defined as systemic hypotension (defined by a decrease in systemic arterial blood pressure of 30 mmHg or more), bradycardia (≤40 bpm), or clinical syncope.

Interventional procedures were performed by two experienced interventional radiologists (including J.L.C., 20 years of experience in radiology service, with more than 200 CAS procedures performed). Patients were treated with unfractioned heparin and two antiplatelet drugs prior to the procedure. Neither systemic anesthesia nor sedative drugs were administered to assess the neurologic function of the patients along the process.

A catheter was positioned in the common carotid artery. For most of the patients, a distal protection device (Spider, EV3, Plymouth, Minn; or Accunet, Guidant, Santa Clara, Calif) was used with different pore sizes (80–130 μm). In some patients, predilation of the ICA lesion was performed by using a 2–4-mm-diameter balloon catheter. A self-expandable stent (Carotid Wallstent, Boston Scientific/Target Therapeutics, Natick, Mass; Carotid Acculink, Guidant; or Precise, Cordis/Johnson & Johnson, Warren, NJ) was placed in the ICA and in common carotid artery, if needed. Postdilation was performed with a 5–6-mm-diameter balloon catheter. The balloons were inflated to a pressure of up to 8 atm. The mean occlusion time was 34.4 seconds ± 15.4 (range, 5–68 sec; $n = 51$).

Imaging Studies

In 55 patients in the treatment group (74.3%), we performed a brain 3-T MR imaging study (diffusion-weighted, fluid-attenuated inversion recovery T2-weighted sequences) the day before the CAS procedure and 24–48 hours after the procedure. Acute lesions were defined (J.L.C.) as hyperintensities on diffusion-weighted images, associated with a reduction of the apparent diffusion coefficient of at least 20%, compared with the unaffected tissue of the opposite hemisphere. No neuroimaging tests were performed in the control groups.

Laboratory Tests

In the CAS group, arterial blood samples were obtained from the common carotid artery immediately before starting the procedure or any manipulation near the atheromatous plaque. After the last injection of contrast material, postprocedure arterial samples were obtained from the same point in the vasculature as the preprocedure blood samples. Simultaneously, pre- and postprocedure venous blood samples were obtained, and then samples were obtained from the peripheral veins at 24, 48, and 72 hours. In the control group that underwent diagnostic cerebral angiography, arterial blood samples were obtained from the common carotid artery before and after finishing contrast material injections for diagnostic purposes. In the coronary group, samples were obtained before and after all the angioplasty and stent placement procedures.

Blood samples were collected in chemistry test tubes, centrifuged at 3000 g for 15 minutes, and immediately frozen and stored at 80°C. Serum levels of glutamate were determined with high-performance liquid chromatography analysis following a previously described method (11). Intra- and interassay coefficients of variation were 1.7% and 2.3%, respectively. Determinations were performed in a laboratory with authors blinded to clinical and neuroimaging data.

Statistical Analysis

Categorical variables are expressed as percentages and were compared with the χ^2 test. Continuous variables are expressed as mean ± standard deviation or median (and quartiles) and were compared by using Student t test, paired t test, Mann-Whitney test, analysis of variance, or Kruskal-Wallis test, as appropriate, after testing normality with the Kolmogorov-Smirnov test. Repeated-measure analysis of variance was used for repeated measures in time. The correlation between continuous variables was performed by using the Pearson or Spearman coefficients, depending on their distribution.

Results

Table 1 shows demographic variables, vascular risk factors, and baseline serum glutamate concentrations in CAS patients and control groups. CAS patients were older and hypertension was more frequent in that group than in the other two groups. The proportion of men was higher in both CAS patients and those who underwent coronary angioplasty and stent placement. The three groups did not show significant differences regarding the rest of the vascular risk factors and glutamate baseline levels. Baseline concentrations of glutamate in arterial (111.1 μmol/L ± 77.6 and 98.9 μmol/L ± 42.4, respectively, for CAS and cerebral angiography group)

Table 1

Patient Characteristics

Characteristic	CAS ($n = 74$)	Cerebral Angiography without Stenosis ($n = 16$)	Coronary Angioplasty and Stent Placement ($n = 20$)	*P* Value
Mean patient age (y)*	68.9 ± 9.3 (45–88)	58.4 ± 17.6 (26–80)	66.1 ± 9.2 (43–80)	.003
Mean age (y)				
Men	68.6 (45–88)	62.0 (44–80)	67.07 (43–80)	NA
Women	70.4 (56–83)	54.9 (26–76)	63.2 (53–71)	NA
Men (%)	81.1	50.0	80.0	.026
Hypertension (%)	75.7	37.5	60.0	.009
Diabetes (%)	27.0	31.2	15.0	.472
Dyslipemia (%)	58.1	43.8	40.0	.268
Smoking (%)	27.0	37.5	45.0	.275
Previous diagnosis (%)				
Asymptomatic	32.4	NA	NA	NA
Ipsilateral transient ischemic attack	31.1	NA	NA	NA
Ipsilateral stroke	36.5	NA	NA	NA
Ischemia at MR imaging	54.1	NA	NA	NA
Mean baseline glutamate (μmol/L)*				
Arterial	111.1 ± 77.6	98.9 ± 42.4	NA	.551
Venous	127.9 ± 113.0	126.6 ± 50.0	123.8 ± 51.5	.987

Note.—Data in parentheses are the range. NA = not available.

* Data are means ± standard deviation.

Figure 1

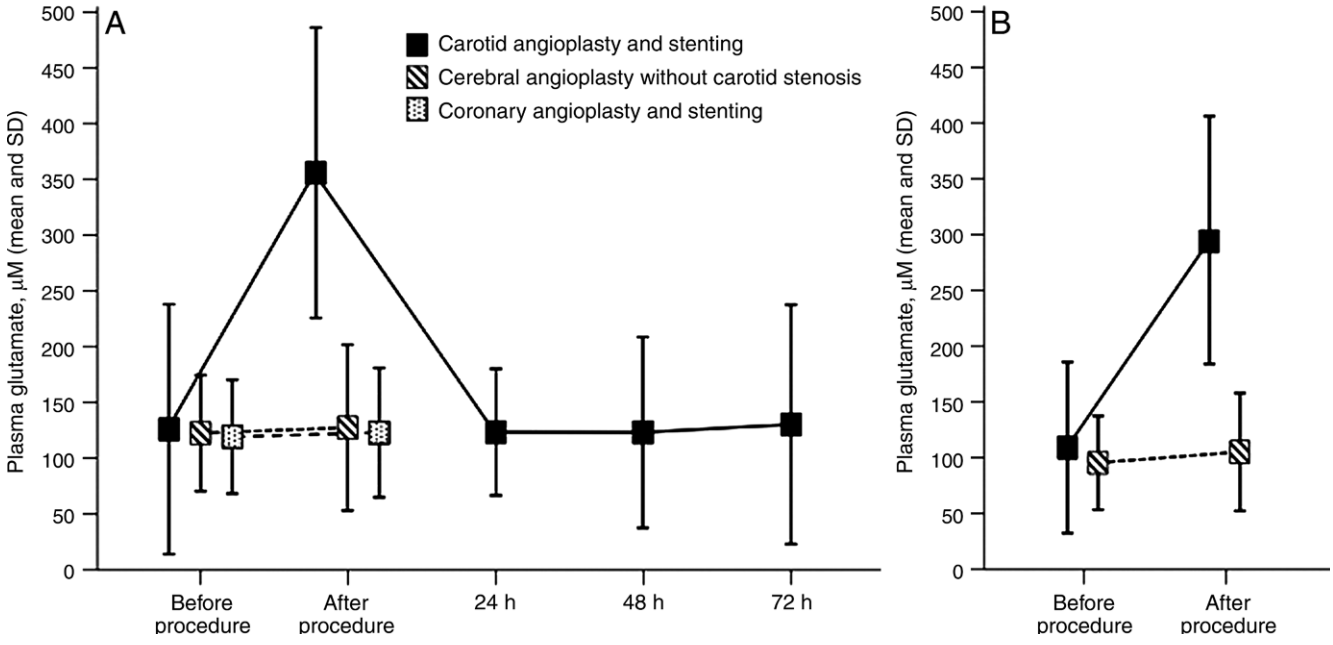

Figure 1: Graphs show evolution of glutamate levels in, *A*, venous blood and, *B*, arterial blood in patients who underwent CAS. *SD* = standard deviation.

and venous (127.9 μmol/L ± 113.0, 126.6 μmol/L ± 50.0, 123.8 μmol/L ± 51.5, respectively, for CAS, cerebral angiography, and coronary angioplasty group) blood were similar ($P = .551$ and .987, respectively).

Arterial and venous glutamate levels showed a sharp increase immediately after the procedure in the CAS

Table 2

Levels of Plasmatic Glutamate in Arterial and Venous Blood in Relation to the Procedures

	Glutamate in Arterial Blood (μmol/L)			Glutamate in Venous Blood (μmol/L)					
Variable	Before Procedure	After Procedure	*P* Value	Before Procedure	After Procedure	*P* Value	24 Hours*	48 Hours*	72 Hours*
CAS	111.1 6 77.6	297.9 6 108.1	<.001	129.7 ± 113.0	354.1 ± 132.8	<.001	129.5 ± 56.8	123.5 ± 81.2	134.8 ± 111.6
CAWS	98.8 6 42.4	103.8 6 52.6	.488	126.6 ± 50.1	130.4 ± 74.1	.710	NA	NA	NA
CAP	NA	NA	NA	123.8 ± 51.5	128.1 ± 58.3	.811	NA	NA	NA

Note.—CAP = Coronary angioplasty and stent placement, CAWS = cerebral angiography without stenosis, NA = not available.

* *P* = .608. Repeated-measure analysis of variance was used to check the values at 24, 48, and 72 hours without significant results.

Table 3

Levels of Plasmatic Glutamate in Relation to the Presence of Cerebral Ischemia

	Glutamate in Arterial Blood (μmol/L)				Glutamate in Venous Blood (μmol/L)			
Variable	Before Procedure	*P* Value	After Procedure	*P* Value	Before Procedure	*P* Value	After Procedure	*P* Value
Without previous ischemic lesions at MR imaging (*n* = 25)	119.4 ± 100.7	.442	290.2 ± 103.1	.865	117.6 ± 72.8	.611	338.1 ± 107.0	.804
With previous ischemic lesions at MR imaging (*n* = 30)	104.2 ± 60.9	…	296.6 ± 113.3	…	104.9 ± 77.6	…	326.9 ± 136.1	…
Without acute ischemic lesions at MR imaging (*n* = 32)	112.4 ± 77.8	.949	283.9 ± 104.4	.189	110.6 ± 80.2	.792	308.1 ± 63.3	.023
With acute ischemic lesions at MR imaging (*n* = 23)	106.9 ± 95.1	…	326.5 ± 117.1	…	111.2 ± 56.8	…	375.3 ± 75.5	…
Uncomplicated (*n* = 41)	123.6 ± 77.1	.536	286.6 ± 120.9	.860	114.3 ± 85.4	.176	313.1 ± 128.6	.045
Ischemic stroke (*n* = 8)	98.3 ± 64.1	…	313.1 ± 126.3	…	113.6 ± 58.9	…	399.9 ± 56.1	…
Hypotension, bradycardia, or syncope (*n* = 21)	96.1 ± 90.3	…	299.6 ± 86.6	…	105.1 ± 60.1	…	318.6 ± 123.3	…

Note.—Unless otherwise indicated, data are means ± standard deviation.

Figure 2

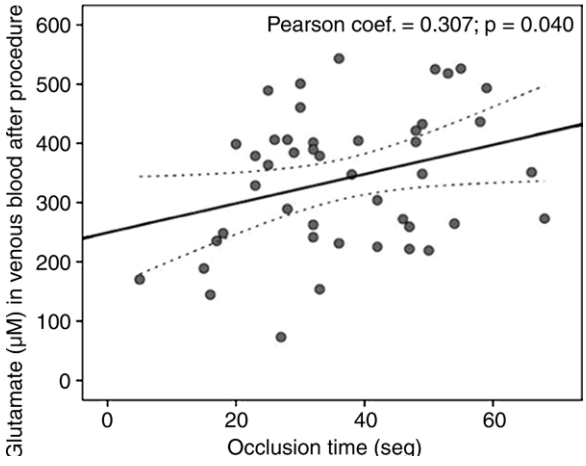

Figure 2: Scatterplot of arterial occlusion time and glutamate plasmatic concentrations in venous blood after finishing the procedures.

group, but did not change in the control groups (Fig 1, Table 2). Increased levels in venous samples decreased into the baseline range at 24 hours and remained stable up to 72 hours after the procedure (Fig 1A). There was a positive correlation between glutamate levels after CAS and occlusion times in the patients analyzed (Pearson coefficient = 0.307, *P* = .040) (Fig 2). Arterial and venous blood glutamate concentrations before and after CAS were similar in all patients (Table 3).

New ischemic lesions were found after CAS in 23 of 55 patients (41.8%) examined with diffusion-weighted MR imaging before and after the procedure. Most of them had small, single (*n* = 13) or multiple (*n* = 6) lesions (< 3 mm diameter) in the ipsilateral territory. Four patients showed large infarctions: watershed in three and territorial in one. Venous blood glutamate concentration after CAS was higher for patients who presented with new ischemic lesions (375.3 μmol/L ± 75.5 vs 308.1 μmol/L ± 63.3, *P* = .023) (Table 3).

CAS was performed without hemodynamic complications in 41 patients (55.4%); 21 patients (28.4%) had episodes of arterial hypotension, bradycardia, or syncope, and eight (10.8%) patients had a focal neurologic deficit with acute ischemic lesions at MR imaging. The latter had higher venous blood glutamate concentrations (399.9 μmol/L ± 56.1) than did patients with hypotension, bradycardia, or syncope (318.6 μmol/L ± 123.3) and those who had no untoward events (313.1 μmol/L ± 128.6), $P = .045$ (Table 3).

Discussion

The increase of glutamate serum levels in patients after CAS is a highly relevant finding, because it has not been described before in patients with such brief periods of brain ischemia. Our results show that molecular changes start very soon after ischemia onset, even without evidence of tissue damage on MR images. In addition, results from control groups allow us to consider brain tissue as the source of glutamate release, being consistent with previous findings in stroke and other diseases of the central nervous system, both in serum and cerebrospinal fluid (12–16).

High glutamate levels have been previously reported after transient ischemic attack and in stroke patients. In those cases, glutamate returned to normal levels at 24 hours, except for stroke progression cases, in which continuous glutamate release was related to enlarging ischemic area (1,2). Our findings match with those previously reported, but in our study patients did not show any neurologic deficit, therefore, it was a brain molecular response even without cellular dysfunction. Asymptomatic patients after CAS and carotid endarterectomy with silent lesions in diffusion-weighted MR images have been previously described (17,18), but in our study even patients with normal MR imaging findings had glutamate high levels.

One limitation of the present study was that all patients who were included were being treated. CAS is a very dynamic procedure, with different characteristics for each patient, so it is difficult to check all potential confounders of these cases. Patients in the control groups were also being treated for other medical problems at the moment of inclusion, so they cannot be easily matched correctly to the treatment group.

These results open new investigation lines in acute stroke. Both in vitro and animal ischemic models can be designed to study molecular changes before tissue damage occurs. Recent studies have suggested that MR spectroscopy could help identify molecular changes in ischemic tissue with normal diffusion-weighted MR findings in acute stroke (19). Following our findings, it would be interesting to investigate how brief ischemic periods could help the brain better tolerate stroke, opening the door to neuroprotection (20,21).

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