Journal of Cerebral Blood Flow & Metabolism (2011) 31, 1376–1377

www.jcbfm.com

Commentary

GOT to rid the body of excess glutamate

Vivian I Teichberg

The Louis and Florence Katz Cohen Professor of Neuropharmacology, Department of Neurobiology, The Weizmann Institute of Science, Rehovot, Israel

Journal of Cerebral Blood Flow & Metabolism (2011) **31,** 1376–1377; doi:10.1038/jcbfm.2011.46; published online 30 March 2011

Two landmark papers from the laboratory of Jose Castillo at the University of Santiago de Compostela in Spain, published in the *Journal of Cerebral Blood Flow and Metabolism* (Campos *et al*, 2011*a, b*), may have a major impact on the future treatment of stroke.

Ischemic stroke is a devastating disorder, often leading to death or long-lasting neurological disability. Tissue plasminogen activator, the main treatment, is only effective for a small population of stroke victims, leaving millions of stroke victims worldwide facing a bleak situation.

In fact, the potential treatment they describe may become standard for a number of other brain pathologies that, like stroke, involve a transient or chronic excess of glutamate in brain fluids. These include epilepsy, dementias (e.g., Alzheimer's disease), multiple sclerosis, Parkinson's disease and other hyperkinetic disorders, amyotrophic lateral sclerosis, pain syndromes, and brain injury; these are responsible for about 1% of deaths and account for almost 11% of the disease burden world-wide.

In the first paper (Campos *et al*, 2011*a*), the authors demonstrate the effectiveness of oxaloacetate—a blood glutamate scavenger—in treating rats with a transient occlusion of the middle cerebral artery (a rat model of stroke). Under the stringent STAIR guidelines (Philip *et al*, 2009), they observed that a bolus intravenous injection of oxaloacetate decreases both blood and brain glutamate levels, causes an 80% reduction in the brain infarct volume, and prevents the development of brain edema. The neuroprotective effect of oxaloacetate is due to the decrease it causes in blood glutamate levels as a result of the activation of a blood-resident enzyme glutamate-oxaloacetate transaminase (GOT) (Gottlieb *et al*, 2003). The latter enzyme causes a reversible reaction wherein glutamate reacts with oxaloacetate to transfer an amino group transforming glutamate into 2-ketoglutarate and oxaloacetate into aspartate.

When glutamate levels in brain fluids are elevated, the activation of blood GOT with oxaloacetate causes an acceleration of a naturally brain-to-blood glutamate efflux driven by the newly established glutamate concentration gradient across the blood–brain barrier capillaries (Gottlieb *et al*, 2003).

In naïve rats, intravenous oxaloacetate was found to accelerate the transfer of radioactive glutamate into the bloodstream after it was injected into the lateral ventricles and to decrease in parallel blood glutamate (Gottlieb *et al*, 2003). The same phenomenon was observed in another supportive study using dual-probe brain microdialysis in which one probe released glutamate and a second probe collected it at a distance of 1 mm (Teichberg *et al*, 2009).

The impressive neuroprotective effect of oxaloacetate has been previously established in a rat model of head injury (Zlotnik *et al*, 2007), but that paper of Zlotnik *et al* (2007) lacked direct evidence—now provided for the first time by Campos *et al* (2011*a*) by their use of magnetic resonance spectroscopy—that blood glutamate scavenging is the direct cause of decrease of glutamate in the brain fluids within the infarcted region. Thus, Campos *et al* (2011*a*) not only provide the final missing proof for the neuroprotective mechanism of blood glutamate scavenging, but also establish its effectiveness for the treatment of experimental stroke.

Of course, rats are not humans and the corresponding dosage of oxaloacetate for a human would be huge, as well as toxic.

The second paper by Jose Castillo's group (Campos *et al*, 2011*b*) makes the jump from rat to human, in a fairly large cohort of several hundred stroke victims admitted to the emergency wards of two different hospitals. Using the same inclusion and exclusion criteria, they revealed two highly significant prognostic parameters for the future outcome of stroke patients in terms of the modified Rankin scale score at 3 months and their infarct size.

High blood glutamate levels (up to three times the normal values) at the time of hospital admission are highly correlated with a poor outcome, confirming previously established results (Davalos *et al*, 1997, 2000), while high blood GOT levels (twice the normal values) at admission are correlated with a good outcome.

Correspondence: VI Teichberg, The Louis and Florence Katz Cohen Professor of Neuropharmacology, Department of Neurobiology, The Weizmann Institute of Science, Rehovot 76100, Israel.
E-mail: vivian.teichberg@weizmann.ac.il
Published online 30 March 2011

The implication of these two papers is that stroke patients' chance of recovery may be significantly boosted by decreasing their blood glutamate levels to about 50% of the normal values (from $\sim$200 μmo/L to $\sim$100 μmol/L)) by bolus intravenous administration of GOT, i.e., to a level of 150 U/L, which is around 3 times the normal range of GOT in clinical labs. This should bring about a decrease in glutamate in the extracellular fluids within and surrounding the infarcted brain region.

Blood glutamate scavengers work only in the blood; they accelerate the natural brain-to-blood glutamate efflux only in those areas of the brain in which glutamate is present in excess (Gottlieb *et al*, 2003).

This treatment is unlikely to have unwanted pathological consequences:

Plasma glutamate fluctuates in any case by about 50% during the circadian cycle (Tsai and Huang 2000), most likely because of the accumulation of glutamate in brain fluids during intense neuronal activity or the REM phases of sleep. GOT also is known to increase naturally, as it does in hepatitis, by several-hundred fold, without leaving any sort of pathology, either transient or permanent.

Submitted papers from our laboratory also show the therapeutic effectiveness of blood glutamate scavenging in experimental models of human glioma, and in experimental models of sporadic and familial amyotrophic lateral sclerosis (Ruban *et al*).

Thus, the stage is now set for conducting clinical trials not only for brain pathologies linked to the presence of excess glutamate in brain fluids, but also because the studies of Castillo and his colleagues hold larger implications: By adding a single test for glutamate/GOT in the routine clinical lab analysis, doctors will gain a new tool for diagnosing stroke and regulating its treatment.

References

Campos F, Sobrino T, Ramos-Cabrer P, Argibay B, Agulla J, Perez-Mato M, Rodriguez-Gonzalez R, Brea D, Castillo J (2011*a*) Neuroprotection by glutamate oxaloacetate transaminase in ischemic stroke: an experimental study. *J Cereb Blood Flow Metab* 31:1378–86 (this issue)

Campos F, Sobrino T, Ramos-Cabrer P, Castellanos M, Blanco M, Rodriguez-Yanez M, Serena J, Leira R, Castillo J (2011*b*) High blood glutamate oxaloacetate transaminase levels are associated with good functional outcome in acute ischemic stroke. *J Cereb Blood Flow Metab* 31:1387–93 (this issue)

Davalos A, Castillo J, Serena J, Noya M (1997) Duration of glutamate release after acute ischemic stroke. *Stroke* 28:708–10

Davalos A, Shuaib A, Wahlgren NG (2000) Neurotransmitters and pathophysiology of stroke: evidence for the release of glutamate and other transmitters/mediators in animals and humans. *J Stroke Cerebrovasc Dis* 9: 2–8

Gottlieb M, Wang Y, Teichberg VI (2003) Blood-mediated scavenging of cerebrospinal fluid glutamate. *J Neurochem* 87:119–26

Philip M, Benatar M, Fisher M, Savitz SI (2009) Methodological quality of animal studies of neuroprotective agents currently in phase II/III acute ischemic stroke trials. *Stroke* 40:577–81

Ruban A, Berkuzki T, Mohar B, Teichberg VI. Blood glutamate scavengers prolong the survival of rats and mice with brain-implanted gliomas. *Current Cancer Drug Targets* (submitted)

Ruban A, Epstein T, Babakin L, Teichberg VI. (-b) Blood glutamate scavenging in animal models of amyotrophic lateral sclerosis. *J Neuroscience* (submitted)

Teichberg VI, Cohen-Kashi-Malina K, Cooper I, Zlotnik A (2009) Homeostasis of glutamate in brain fluids: an accelerated brain-to-blood efflux of excess glutamate is produced by blood glutamate scavenging and offers protection from neuropathologies. *Neuroscience* 158:301–8

Tsai PJ, Huang PC (2000) Circadian variations in plasma and erythrocyte glutamate concentrations in adult men consuming a diet with and without added monosodium glutamate. *J Nutr* 130:1002S–4S

Zlotnik A, Gurevich B, Tkachov S, Maoz I, Shapira Y, Teichberg VI (2007) Brain neuroprotection by scavenging blood glutamate. *Exp Neurol* 203:213–20