



© 3D4Medical.com/Getty Images A glutamate surge radiates out from the area of original damage, and kills neurons in nearby areas.

Protecting the Brain from a Glutamate Storm

By Vivian Teichberg, and Luba Vikhanski

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When a stroke or head injury releases a flood of the chemical messenger glutamate, the excess glutamate leaves damaged neurons in its wake. Israeli scientist Vivian Teichberg, Ph.D., has developed a new method that may protect the brain from this destruction by harnessing the brain's natural ability to keep glutamate levels in check.

The human brain is packed with a substance that needs to be treated like a handle-with-care explosive. Glutamate, one of the most abundant chemical messengers in the brain, plays a role in many vital brain functions, such as learning and memory, but it can inflict massive damage if it is accidentally spilled into brain tissue in large amounts.

Glutamate flow in the brain is normally kept in check by a system of dam-like structures, which release a trickle of the substance only when and where it is needed. But burst a dam—as happens in stroke, head trauma, and some other neurological disorders—and the treacherous messenger floods the brain. The surge of glutamate radiates out from the area of original damage, and kills neurons in nearby areas. The expanded damage can leave in its wake signs of impaired brain function, such as slurred speech and shaky movement.

Depending on the severity and location of the stroke or head trauma, recovery can be slow and incomplete. Now new hope is coming from a completely new approach to protecting the brain against the ravages of injury and disease. It consists of “mopping up” excess glutamate by boosting a natural process that the healthy brain already uses to safeguard itself from a glutamate overdose. If this concept is borne out in clinical trials, it might be helpful in treating a variety of acute and chronic brain insults and diseases.

Inside the Glutamate Storm

The amino acid glutamate is the major signaling chemical in nature. All invertebrates (worms, insects, and the like) use glutamate for conveying messages from nerve to muscle. In mammals, glutamate is mainly present in the central nervous system, brain, and spinal cord, where it plays the role of a neuronal messenger, or neurotransmitter. In fact, almost all brain cells use glutamate to exchange messages. Moreover, glutamate can serve as a source of energy for the brain cells when their regular energy supplier, glucose, is lacking. However, when its levels rise too high in the spaces between cells—known as extracellular spaces—glutamate turns its coat to become a toxin that kills neurons.*

As befits a potentially hazardous substance, glutamate is kept safely sealed within the brain cells. A healthy neuron releases glutamate only when it needs to convey a message, then immediately sucks the messenger back inside. Glutamate concentration inside the cells is 10,000 times greater than outside them. If we follow the dam analogy, that would be equivalent to holding 10,000 cubic feet of glutamate behind the dam and letting only a trickle of one cubic foot flow freely outside. A clever pumping mechanism makes sure

this trickle never gets out of hand: When a neuron senses the presence of too much glutamate in the vicinity—the extracellular space—it switches on special pumps on its membrane and siphons the maverick glutamate back in.

This protective pumping process works beautifully as long as glutamate levels stay within the normal range. But the levels can rise sharply if a damaged cell spills out its glutamate. In such a case, the pumps on the cellular membranes can no longer cope with the situation, and glutamate reveals its destructive powers. It doesn't kill the neuron directly. Rather, it overly excites the cell, causing it to open its pores excessively and let in large quantities of substances that are normally allowed to enter only in limited amounts.

One of these substances is sodium, which leads to cell swelling because its entry is accompanied by an inrush of water, needed to

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dilute the surplus sodium. The swelling squeezes the neighboring blood vessels, preventing normal blood flow and interrupting the supply of oxygen and glucose, which ultimately leads to cell death. Cell swelling, however, is reversible; the cells will shrink back once glutamate is removed from brain fluids. More dangerous than sodium is calcium, which is harmless under normal conditions but not when it rushes inside through excessively opened pores. An overload of calcium destroys the neuron's vital structures and eventually kills it.

Regardless of what killed it, the dead cell spills out its glutamate, all the vast quantities of it that were supposed to be held back by the dam. The spill overly excites more cells, and these die in turn, spilling yet more glutamate. The destructive process repeats itself

over and over, engulfing brain areas until the protective pumping mechanism finally manages to stop the spread of glutamate.

That's precisely what happens in stroke or head trauma, each of which begins with a sudden injury to brain tissue that ensues when a blood vessel is ruptured or blocked by a blood clot. In trauma, the damage is inflicted by a blow to the head. If the damaged area, called the core, is small and not located in a vital region of the brain, it might not cause major harm. However, because the dead cells in the core spill out their glutamate, the core often becomes the center of a glutamate spill. While the center itself cannot be saved, the secondary damage triggered by glutamate release from damaged or dying brain cells could theoretically be prevented or at least limited, and perhaps even reversed. Medical management can help to prevent further damage, but effective neuroprotective drugs have, so far, been hard to come by.

Why Drugs Fail

Scientists may argue about the relative roles of glutamate and other chemicals, but research overwhelmingly suggests that excess release of glutamate is one of the earliest and most crucial steps in the destructive cascade of events in the traumatized brain and that glutamate's relationship to neurological damage is that of cause and effect. Furthermore, physicians have established that the chances for recovery from stroke or head trauma are better the lower the levels of glutamate are within the spaces between brain cells. These extracellular spaces are where brain cell axons (communication cables) send signals from one brain cell to another. Conversely, the higher the glutamate levels in these extracellular spaces, the poorer the outcome from stroke or head injury.

However, in focusing just on glutamate's destructive potential, research has overlooked the chemical's role as the brain's premier messenger, and that omission may be a key to why glutamate-blocking drugs, which prevent glutamate from over-exciting brain cells,

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fail in clinical trials. Entirely blocking glutamate's activity in the brain after stroke or trauma may not be such a good idea: Along with stopping glutamate's demolition activity, the blocking shuts down all messages carried by glutamate, and these messages might be critical for the patient's recovery, as they appear to be essential for the initiation and maintenance of the brain's repair mechanisms.¹ In other words, it's possible that glutamate-blocking drugs have failed to promote recovery after stroke because they have been inadvertently blocking the brain's natural self-repair mechanisms.

Another reason for the failure of glutamate blockers might be timing. In rats, glutamate levels are excessively high for only about two hours after trauma, and a single injection of glutamate blockers during this time can promote recovery. In humans, in contrast to rats, the surge of glutamate may persist for hours or even days and therefore needs to be dealt with over a longer period of time. Yet in most clinical trials of stroke

treatments, glutamate blockers were given just once. These blockers, as well as the other drugs, might have failed because even if they

had a positive effect, they didn't take care of the glutamate spill, which continued to wreak its havoc after the drug had cleared from the brain.

Then we have the problem of delivering the drug to the area of brain damage. Drugs intended to protect the brain are purposely designed to enter the bloodstream and cross the blood-brain barrier, the impervious layer of cells that lines the walls of the brain's blood vessels and prevents most substances from entering our most well-guarded organ. However, in stroke and head trauma, the supply of blood to the damaged brain area is impaired because blood vessels are blocked, ruptured, or constricted. Therefore, even the most effective drugs are prevented from producing their beneficial effect because they cannot get to the site of injury.

Moreover, moving from rat research to clinical trials in humans presents an overall challenge. Unlike young and uniform laboratory animals, each human patient requiring a stroke or brain trauma medication is unique, and this variability makes it difficult to determine whether the drug is indeed effective. Strokes tend to occur when people are older and might have diabetes, heart disease, or other conditions that can interfere with a drug's activity in unpredictable ways. Other issues can arise in connection with head trauma, such as the presence of alcohol in the blood or brain of accident victims, which can also affect a drug's action.

Finally, developing a drug for stroke or brain trauma poses a major challenge because the drug must do significantly better than natural brain repair mechanisms, yet nature already does a reasonably good job of post-traumatic brain repair. So far, only the clot-dissolving drugs called tissue plasminogen activator (tPA) have met the United States Food and Drug Administration's requirements for both safety and effectiveness.

A New Approach

The disappointing performance of neuroprotective drugs for treating stroke in clinical trials was the starting point for recent research at the Weizmann Institute in Israel that has led to a radically new approach to battling excess glutamate. My (Vivian Teichberg's) research team has developed an innovative experimental therapy relying on the natural pumping mechanism that normally protects the brain against excess glutamate.

As mentioned earlier, much of this pumping removes glutamate from the extracellular spaces between brain cells by siphoning glutamate back into these cells—mainly the neurons—and their supporting cells, the glia. But an additional route for this protective mechanism has received much less attention from scientists. Glutamate pumps are also present on the outer surface of the brain's blood vessels, the surface facing the brain tissue. The fact that glutamate is being pumped from the brain into the blood circulation was demonstrated more than 45 years ago. This was observed back in the 1960s by Soll Berl, M.D., from the New York State Psychiatric Institute, who found that if a small trace of radioactive glutamate is injected into the brain, it shows up outside the brain, in the peripheral blood, within one minute.

After we repeated Berl's experiment and confirmed his findings, our next goal was to harness this brain-to-blood pumping process for brain-protective purposes. Such a procedure has great therapeutic potential,

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because brain tissue is densely meshed with tiny blood vessels called capillaries. The human brain has more than 100 billion capillaries, with a total length of about 400 miles and a total surface area of 130 square feet—and a huge number of glutamate pumps! Still, toxic glutamate spills occur in stroke, head trauma, and many neurological diseases, which shows that this protective arsenal does not always rise to

the task when things go badly wrong.

The question was how to increase the pumping of glutamate out of the brain and into the bloodstream to protect the brain. Shutting down a cellular pump is easy; making it work faster and better is much more tricky. As is true for many natural processes perfected by eons of evolution, these pumps already work very well, so that enhancing such a process is no mean feat.

Our answer came from exploring the secrets of brain-to-blood pumping. It turned out that two efficient yet disarmingly simple mechanisms are in play. First, glutamate is pumped into the cells that make up the blood vessel wall. This step is performed by the glutamate pumps on the outer side of the brain's blood vessels, the side that comes into contact with the brain tissue. Because the blood vessel wall cells are very small in size, glutamate concentration inside them quickly builds up to very high levels, much higher than the chemical's concentration in the blood. That leads to the second step of the process, which stems from basic chemistry: Glutamate naturally flows by diffusion from areas of high concentration (in blood vessel wall cells) through the blood vessel wall into the circulating bloodstream, where the concentration is lower.

This insight led to the idea of accelerating the naturally occurring brain-to-blood pumping by lowering glutamate levels in the circulating blood. The hypothesis was that a larger difference in glutamate concentration would enhance the driving force for the chemical's removal, and more glutamate would flow out of the brain and into the circulating blood.

That was indeed what happened. We made use of the fact that certain blood enzymes can reduce blood glutamate levels by transforming glutamate into a different substance—a transformation that takes place in the presence of increased levels of certain compounds. When these compounds were injected into the bloodstream of rats, this transformation rapidly occurred and the animals' blood glutamate levels dropped by 50 percent—and so did glutamate levels in the brain's cerebrospinal fluid. Thus, the experiment strongly suggested that lowering glutamate levels in the circulating blood was an effective strategy for kicking the glutamate pumps' activity into high gear in order to “mop up” toxic glutamate spills in the brain.²

The next task was to test whether clearing excess glutamate from the brain by this method would protect the brain from glutamate's deleterious effects. In experiments in rats with traumatic brain injury, a natural compound called oxaloacetate, which reacts with the blood enzyme glutamate-oxaloacetate transaminase, was used to scavenge blood glutamate. Rats with brain injury treated by this method regained normal body function and recovered faster and more fully than rats with the same brain injury that received no medication to lower glutamate levels.³

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We are currently developing non-invasive ways of assessing brain glutamate levels in humans that should help implement the new approach in clinical practice. Drilling a

hole in a person's skull just to measure the glutamate is hardly an attractive prospect, but magnetic resonance spectroscopy, an analytical method that reveals the presence of various brain chemicals through the skull in a non-invasive manner, might offer a viable alternative.

Avoiding Problems

The proposed Weizmann Institute concept circumvents many of the problems encountered by previous brain-protecting drugs. Most of the trials of agents to modify excess glutamate were stopped because of side effects, primarily psychosis, but the natural compounds we tested are safe and cause no side effects. In addition, our method involves no concern about drugs crossing the blood-brain barrier or entering the brain despite impaired blood circulation. The added compounds act within the blood in order to protect the brain, rather than targeting the brain directly.

Nor does a concern exist about interfering with glutamate's beneficial action. Rather than blocking glutamate inside the brain, the method clears the excess chemical away from the brain into the blood, where it can no longer do harm. At the same time, the amount of glutamate needed for conveying messages of brain repair can remain in the brain.

No less important, this method aims to protect the brain by going to the root of the problem: preventing the glutamate storm. Whether it can be used alone, however, or in combination with other therapies, will depend on the timing. If it is applied immediately after stroke or injury, cleaning the brain of excess glutamate could be sufficient for preventing all subsequent problems, and no other drugs may be necessary. In many cases, however, the drugs cannot be given immediately. Strokes sometimes occur during sleep, and by the time the person wakes up and discovers the damage, precious time has been lost. Moreover, both strokes and head traumas can occur in areas where transportation to the hospital can take many hours. In such cases, a glutamate “mop-up” will still be relevant, but it may need to be accompanied by a “cocktail” of other drugs to counter the various types of damage already inflicted by the glutamate spill.

Toward Wider Applications

If proved effective, this new method may be helpful in treating not only stroke and head trauma but a variety of acute and chronic conditions—ones that involve the death of brain cells followed by a harmful glutamate glut. For example, a type of brain inflammation known as bacterial meningitis is successfully treated by antibiotics but often leads to neurological problems, such as hearing impairment and cognitive deficits, believed to be caused by excess glutamate. Toxicity from excess glutamate is thought to be a component of other conditions as diverse as hypoglycemia, some brain cancers, damage to a newborn's brain caused by interrupted oxygen supply during delivery, and exposure to nerve gas. Glutamate is probably also involved in chronic nerve damage in such conditions as glaucoma, amyotrophic lateral sclerosis (ALS), and HIV dementia. Though the mechanisms of excess glutamate release in these conditions are more obscure compared with acute brain insults, clearing surplus glutamate from the brain might be beneficial.

The method developed at the Weizmann Institute will soon be applied in clinical trials to be conducted by an Israeli biotechnical company. They will be designed to test whether the approach can protect the human brain against glutamate damage as well as it protects the brains of injured rats. Because the method works with nature and not against it, we hope that it will succeed where many others have failed.

* The glutamate in MSG (monosodium glutamate), used in some foods, is related to brain glutamate but does not appear to get into the brains of adults very well. It can get into the brains of infants and be toxic to brain cells, however, which is why the FDA has not approved it for use in baby food.

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About Vivian Teichberg

Vivian I. Teichberg, Ph.D., a professor of neurobiology at the Weizmann Institute of Science in Rehovot, Israel, studies the physiological and pathological roles of glutamate in brain. He was among the first to isolate and study a receptor protein to which glutamate binds in the brain, and to solve this receptor's primary structure. He is the recipient of several prizes, including the Somach Sachs Memorial Award and the French Academy of Sciences Professorship, and holds the Louis and Florence Katz-Cohen Professorial Chair of Neuropharmacology. He can be reached at vivian.teichberg@weizmann.ac.il.

About Luba Vikhanski

Luba Vikhanski, a freelance science journalist who specializes in covering biomedical research, also works as a science writer in the Publications and Media Relations Department of the Weizmann Institute. She is the author of *In Search of the Lost Cord: Solving the Mystery of Spinal Cord Regeneration* (Dana Press and Joseph Henry Press, 2001) and of *A Well-Informed Patient's Guide to Breast Surgery*, which won the 1993 Rose Kushner Award of the American Medical Writers Association. Her news stories and feature articles have appeared in publications including *Scientific American*, *Nature Medicine*, the *New York Times*, and the *Jerusalem Post*. She can be reached at luba.vikhanski@weizmann.ac.il.