A Lot of "Excitement" About Neurodegeneration

Suggestive data indicate that "excitotoxicity" could play a role in Alzheimer's and in Parkinson's

"GOING SOFT IN THE HEAD" IS THE MOST terrifying of the possibilities inherent in growing old. Gray hair, wrinkles, failing eyes, and arthritis seem like a day at the beach compared to losing the ability to think or remember. The diseases that cause such a loss—Alzheimer's and Parkinson's—baffle not only patients but also researchers trying to understand them. "The neurodegenerative diseases of aging are one of the great brick walls in neurology—they are just the hardest nuts we have to crack," says neurologist J. William Langston of the California Parkinson's Foundation in San Jose.

But a recent conference in Philadelphia revealed that researchers have a new conceptual nutcracker that might ultimately help break open these tough nuts.* That is the idea that normal brain chemicals—the excitatory amino acid neurotransmitters glutamate and aspartate—released in abnormal amounts could be the agents that kill neurons in neurodegenerative diseases. There is now some experimental evidence available to support the idea that "excitotoxins" have a role in Huntington's chorea as well as Parkinson's disease and Alzheimer's dementia—although in all these cases precise mechanisms remain speculative. If the excitotoxin hypothesis is true, it could lead to new strategies for blocking brain degeneration.

According to conference cochair Langston, the Philadelphia meeting was the first designed to bring together the full range of scientists working on neurotoxicity and degenerative disease. Twenty years ago, says Langston, "doctors mostly thought of neurotoxins as causes of only relatively obscure diseases—a rare case of mushroom poisoning here, or a case of anesthetic toxicity there." But as researchers have learned to use neurotoxins as tools for probing neuron function and creating animal models of human diseases, they have begun to see connections between the poisoning of neurons and the degeneration that takes place in diseases like Alzheimer's.

In normal brain function, glutamate and aspartate are released from the terminals of one neuron and bind to receptors on the surface of adjacent neurons. Such excitatory amino acids (EAAs) exist in high concentration in every part of the brain, and play a vital role in almost all brain processes. But they also have a darker side, known as excitotoxicity: Abnormally high levels of stimulation of the EAA receptors triggers a destructive cascade of events that can kill neurons en masse.

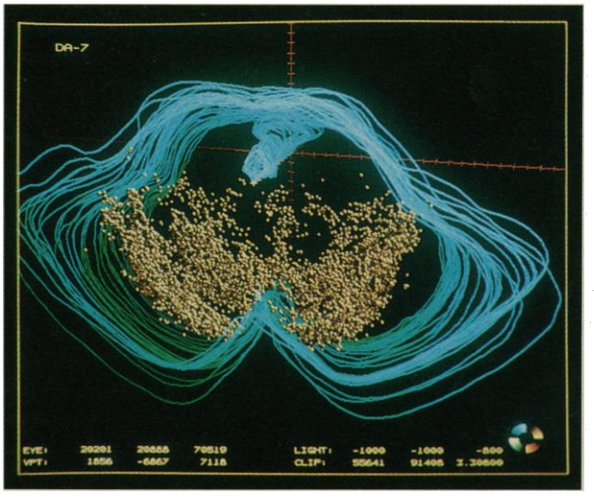
According to John Olney of Washington University in St. Louis, who first described excitotoxicity in 1969, researchers first assembled a strong case implicating abnormal release of glutamate and aspartate as the immediate cause of brain damage in stroke and seizure. Adds Olney, who has been a key player in the development of excitotoxin research: "When we learned that there are molecules in the brain that have the potential to damage neurons, it made sense to think about how they might play a role in neurodegeneration." Such thinking has now begun to pay off in intriguing experimental evidence for excitotoxins in the neurodegenerative diseases.

According to Langston, the fact that researchers can use excitotoxins to mimic the pattern of neural destruction seen in Huntington's chorea gives them reason to believe excitotoxins are involved in this genetic disease—although the case is far from open-and-shut. People who inherit the gene for Huntington's gradually lose voluntary control of their muscles, beginning when they reach middle age, as the disease slowly kills a specific set of neurons in the basal ganglia of the brain.

In the 1980s, Robert Schwartz of the University of Maryland and Flint Beal of Harvard University showed that quinolinic acid (a normal brain chemical, similar to glutamate, that can bind to and stimulate some EAA receptors) can reproduce some of the effects of Huntington's in monkey brains, killing and sparing the same pattern of neurons. "This raises the possibility that the genetic flaw in Huntington's somehow orchestrates the damage through an endogenous excitotoxin," says Langston. Although quinolinic acid itself may not be the culprit, researchers are pursuing this clue, hoping to find the actual guilty party, which could well be an excitatory amino acid.

One of those in pursuit is Olney himself, who presented a provocative hypothesis at the Philadelphia meeting—that the actual neural assassin in Huntington's is L-dopa, an intermediate in the biosynthesis of dopamine. In 1990 Olney showed that exposure to excess L-dopa can kill neurons in the test tube and that specific chemical blockers of EAA receptors can interrupt the effect. Many of the dopamine neurons in the brain terminate on the neurons in the corpus striatum that die in Huntington's. "If there were a defect in the conversion of L-dopa to dopamine, L-dopa would accumulate at the nerve terminals, leak out, and kill the nearby cells in the striatum by an excitotoxic mechanism," he says.

But that's just the first blow in a double whammy. In addition, says Olney, there's evidence that dopamine neurons regulate the activity of excitatory neurons that terminate on the striatum. If the dopamine-containing neurons were unable to do their job, those excitatory neurons could release too much of their excitatory transmitter—glutamate—onto the cells already hyperexcited by L-dopa. "This could catch these cells in a double bind," says Olney, "and explain why these particular cells die in Huntington's."



The case for the involvement of excitotoxins in Parkinson's disease is also not airtight, but it is intriguing, says Stanford neurologist Dennis Choi. Parkinson's starts with a mild hand tremor, progresses to increased difficulty in movement, and leads ultimately to death. The role some researchers are proposing for excitotoxins in Parkinson's stems from two main lines of work in animal models and cell culture.

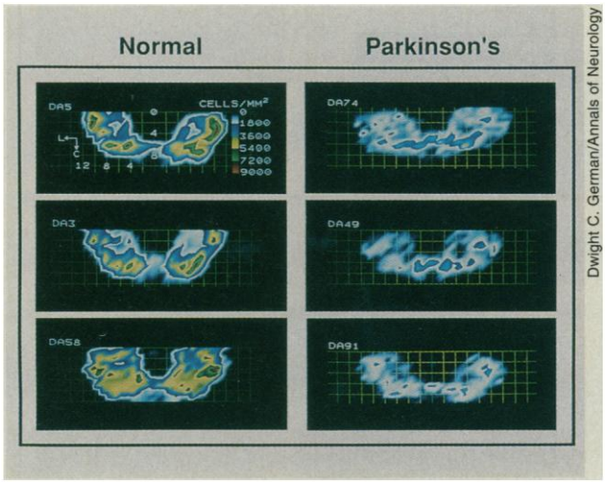
*"Neurotoxins and Their Potential Role in Neurodegeneration," sponsored by The New York Academy of Sciences, held 6–8 May in Philadelphia.

The first line of evidence comes from data on what happens when EAA receptors are blocked. For some time, researchers have been gathering data showing that at least three different toxins can mimic the destruction of dopamine neurons seen in Parkinson's—and sometimes the symptoms of the disease as well. The chemicals 6-hydroxydopamine and 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) selectively kill many of the same neurons that die in Parkinson's and also produce the symptoms of Parkinson's in primates. (These properties of MPTP came to light in 1982, when several heroin addicts suddenly came down with Parkinson's symptoms after taking a tainted, illicitly brewed, synthetic opiate.) The third type of toxin—amphetamines—is less selective and does not produce symptoms.

The first inkling that these data could point to underlying excitotoxicity came in 1989, when Richard Heikkila and Pat Sonsalla at the Robert Wood Johnson School of Medicine in Piscataway, New Jersey, showed that in mice, an EAA receptor blocker called MK-801 can protect dopamine neurons from damage by amphetamines. Then, in January of this year, a report in *Nature* from Lechoslaw Turski in Germany presented data indicating that MK-801 could also protect dopamine neurons in rat brains from damage by direct injection with MPP+, the active metabolite of MPTP.

Turski's results were the subject of considerable discussion—and difference of opinion—at the conference. Some participants criticized the data, saying that they may not apply to human beings, in part because rats are less sensitive to the toxin and that therefore the doses of MPP+ needed to cause brain damage in rats are extremely high. Furthermore, Sonsalla reported that, using a somewhat different experimental approach, she could not find a similar effect. But Giovanni Corsini and his colleagues from the University of Pisa in Italy reported in a poster that low doses of MK-801 can protect dopamine neurons in monkeys from MPTP damage. And Langston argued that if Corsini's data hold up, it could well help nail down the connection between Parkinson's and EAAs.

Even if that doesn't happen, another line of evidence seems to link excitotoxicity and Parkinsonism. The mechanism in neurotoxic models for the disease and the action of excitotoxins may both involve production of free radicals: hyper-reactive molecules that can attack proteins, nucleic acids, or lipids that have the misfortune to be nearby. "The free-radical theory in Parkinson's has been kicked around since the early 1970s, and just will not go away," says Langston.



Dwight C. German/Annals of Neurology

Going dotty. *Gold spheres* (left) *indicate the normal distribution of dopaminergic neurons in the human midbrain. Maps above show that these neurons are markedly reduced in Parkinson's patients within the midbrain structure called the substantia nigra.*

The normal metabolism of dopamine might generate free radicals in a number of different ways, and those destructive molecules may contribute to the cumulative dopamine-neuron damage in Parkinson's. "Over the long term," says Langston, "dopamine may just be too hot to handle because of its tendency to generate destructive free radicals."

There is some indication that this line of work is slowly converging with that on excitotoxicity. For example, Choi noted in Philadelphia that certain molecules capable of reducing the formation of free radicals, or scavenging them once they have been generated, can decrease glutamate toxicity in primary cultures of brain neurons. This finding, says Choi, implies that the mechanism by which glutamate and other excitatory amino acids do their damage may overlap with the havoc wrought by the dopamine system.

The clues linking excitotoxicity to Alzheimer's are sketchier than the corresponding data for Parkinson's, but they are suggestive enough that a number of labs are beginning to follow them up. One clue stems from the similarity between Alzheimer's and dementia pugilistica—a syndrome that boxers get from too many blows to the head. (Its most famous victim is Muhammad Ali.) Some of the outward symptoms of the syndrome resemble Parkinson's. But the histology of the disease—tangled, malformed neurons and the accumulation of deposits of a protein called beta amyloid—is much like that seen in Alzheimer's, according to Dennis Selkoe of Harvard University Medical School.

As Olney pointed out at the meeting, there is an interesting recent finding that links head injury, Alzheimer's, and excitotoxicity. It has been shown that a blow to the head of a rat can result in an outpouring of excitatory amino acids similar to the ones seen in seizures and stroke. And, as Selkoe notes, "severe head injury is one of the few nongenetic risk factors for Alzheimer's identified to date."

Selkoe also pointed to new work by Carl Cotman of the University of California at Irvine that suggests excitotoxicity could have a role in Alzheimer's pathology. Specifically, Cotman's work indicates that beta amyloid protein can damage healthy neurons through an excitotoxic mechanism. He and his colleagues find that when they incubate cultured neurons in the presence of beta amyloid, the neurons become more susceptible to toxicity by EAA receptor agonists.

Intriguing as these results are, Cotman insists that it's still too early to tell whether excitotoxicity is a primary or a secondary component of the disease process in Alzheimer's. "Alzheimer's may be caused by a combination of different risk factors," he says. "They might not be serious by themselves, but if they happen to come together, you can get massive damage by excitotoxins."

If Parkinson's and Alzheimer's do involve excitotoxic mechanisms, researchers may be able to develop "neuro-protective" strategies. The trick will be to find drugs that can block the excitotoxic mechanisms without disrupting vital brain processes. In fact, drug manufacturers have labored for years to bring EAA receptor blockers to market for treatment of stroke and seizure—but the toxic side effects of the drugs have been a stumbling block.

It will be some time before researchers know whether glutamate and aspartate are really guilty as charged. "The Philadelphia conference was a bit like making bread," says Langston. "We took people from all different fields of neurotoxicology, mixed and stirred for three days, and now we have to wait for the loaf to come out of the oven." By the time it emerges, it could be a remarkably nourishing scientific concoction.

■ ROBERT TAYLOR

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