Excitotoxicity and Neuroprotection

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Issue: *Excitatory neurotransmission is a normal physiologic process mediated by the neurotransmitter glutamate. Too much glutamate release can be destructive and literally excite a neuron to death in a process called* excitotoxicity. *Blocking this process may be neuroprotective and prevent brain disorders mediated by excitotoxicity.*

Can a neuron be excited to death? Some interesting new findings about glutamate suggest that this excitatory neurotransmitter not only talks to neurons, but can also scream at them, strangle their dendrites, and even assassinate them.[1–7]

One of the key glutamate receptors is called NMDA, named after its selective ligand *N*-methyl-D-aspartate.[1,2] Once glutamate binds to its NMDA receptor, this opens an ion channel in the neuronal membrane so the nerve can drink calcium. Sipping calcium is exciting to a neuron and a normal reaction when glutamate is speaking pleasantly.

Take-Home Points

- Excitotoxicity may be how the brain discards useless connections or prunes poorly functioning neurons
- Angry neurons release glutamate if provoked by poisons, suffocation, or genetic programs
- Glutamate may be the "hit-man" who assassinated neurons in stroke, Alzheimer's disease, and other neurodegenerative disorders, possibly including schizophrenia
- Antagonists to key glutamate receptors may arrest the assassin and prevent neuronal murder

Too much glutamate can be hazardous to your health

When glutamate screams at a neuron, it reacts by drinking more calcium. Imbibing too much calcium can anger intracellular enzymes, which then generate nasty chemicals called free radicals.[1,3–6] A small commune of free radicals can crash the chemical party in the postsynaptic dendrite and strangle it.

Why would the neuron allow this to happen? It is possible that the brain needs this excitotoxic mechanism so that glutamate can act as a gardener in the brain, pruning worn out branches from dendrite trees so that healthy new sprouts might prosper. However, this also equips glutamate with a powerful weapon that can be misused to cause various pathologic states.[1,3–6]

When glutamate decides to act as an abusive bully, neurons may seize, panic, become manic, or become psychotic. Furthermore, such symptoms of calcium intoxication may be followed by an unfortunate glutamate hangover in the form of destroyed dendrites that can never be excited again.

Glutamate as endogenous assassin

At the far end of the excitotoxic spectrum, glutamate's molecular mischief can run rampant and actually murder entire neurons by overwhelming calcium poisoning and free-radical mayhem.[1,3] Certain illnesses such as Alzheimer's disease, Parkinson's disease, Lou Gehrig's disease (amyotro-

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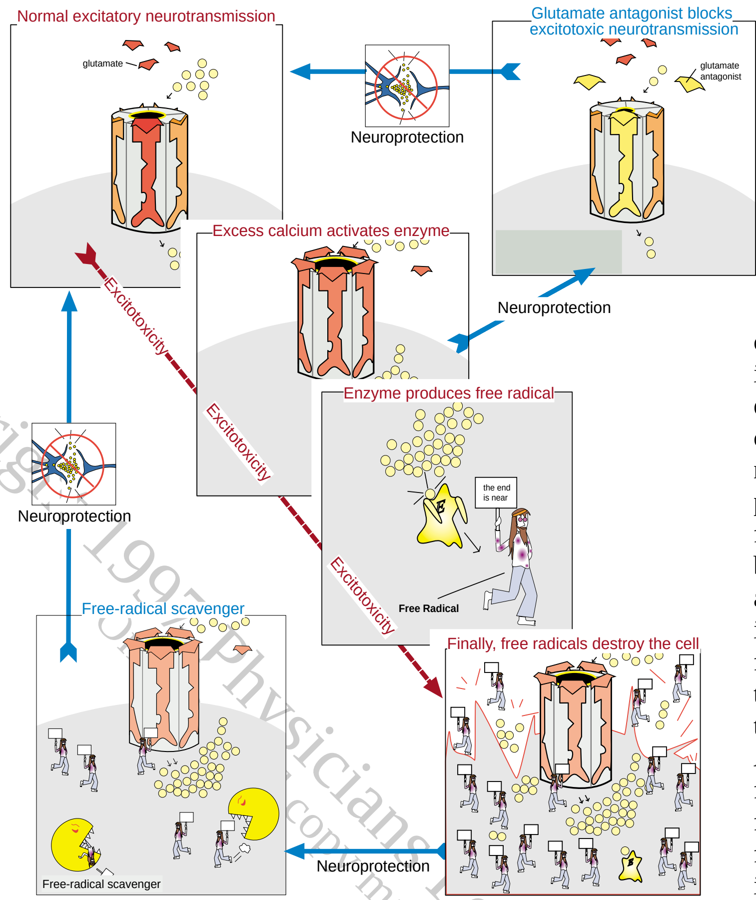

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phic lateral sclerosis), and even schizophrenia may hire glutamate as a methodical assassin, eliminating a whole subpopulation of pre-designated neurons.[7] This is a systematic process consistent with the pace of such neurodegenerative disorders. In the case of stroke, glutamate may form an army of hit-men, and then massacre an entire region of distressed ischemic neurons in the midst of a catastrophic molecular mess.[3]

In summary, glutamate's actions can range across a vast spectrum. It can be a friendly neuronal conversationalist or a screaming hypothetical mediator of symptoms of mental illness. After an abusive tirade, glutamate may even strangle the dendrite it excited. As excitotoxicity escalates, glutamate can become a serial murderer of neurons, wiping them out in a devastating cumulative process over months and years. At an extreme, glutamate is a mass murderer, wreaking the destruction of localized neurons during the chaos of stroke.

Can the brain be rescued or protected?

At least two approaches to collaring glutamate are showing promise.[1,3–6] The first is to protect the neuron from drinking too much calcium by blocking NMDA receptors with antagonists. Thus, neurons are allowed to quench their thirst in normal excitatory neurotransmission, but not guzzle so much calcium that they become excitotoxically inebriated. Numerous NMDA antagonists are able to mitigate neuronal death, including ischemic stroke. Clinical testing of such compounds will be rapidly accelerating in the near future. Such approaches are deemed *neuroprotective* since they arrest glutamate before it can assassinate any more neurons.

Another approach to developing treatments for illnesses that may be mediated by excitotoxicity is to rescue the cellular machinery once glutamate's cascade of doom has been activated. Thus, free-radical scavengers are being developed that neutralize pesky free radicals. Certain chemicals can do this including vitamin E and experimental agents called lazaroids (so-named because they purport to raise neurons from the dead, like the biblical Lazarus). These and other agents are being developed, especially for slow neurodegenerative conditions such as tardive dyskinesia and Alzheimer's disease. As free radicals may be a final common pathway for cellular demise, ranging from atherosclerosis to dementia, the race to discover clinically effective scavengers of these destructive free-radical devils is proceeding fast apace.[1,3–7] ◆

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