NASCIC
SCI RESEARCH
ADVOCACY COURSE

Module 6 – Neuroprotection

Stopping Excitotoxicity (over-excitation of neurons)

Researchers are studying several ways to prevent or stop glutamate excitotoxicity, building on basic research that has helped explain how excess glutamate leads to the death of otherwise healthy cells. So far, researchers have shown that:

- After an SCI, glutamate spills out of damaged neurons and is pumped out of glial cells, leading to a rapid increase that overwhelms the body's normal balancing mechanisms. **[I could see this as the first panel of a three-panel arch. In this one, neurons are breaking apart and releasing dots representing glutamate. And glial cells are spitting glutamate out through pores in their surfaces.]**
- Excess glutamate binds to receptors called NMDA or AMPA on the surface of other nearby neurons and glia, which causes those receptors to become over-stimulated. **[This bullet and the next one describe the second panel, which shows the glutamate released in the first panel sticking to receptors on the surface of healthy neurons and glia that are close to the damaged cells in panel one. When glutamate sticks to these receptors, they open like portals, and allow calcium and sodium to rush into the insides of these healthy cells.]**
- Over-stimulated NMDA or AMPA receptors open channels in the cell membranes that allow excess levels of sodium and calcium to enter the cell.
- Excess sodium and/or calcium in turn triggers the production of free radicals; production of digestive enzymes that break down proteins and other large molecules; apoptosis (also called programmed cell death); or cell rupture. **[In the third panel, the cells that are now full of calcium and sodium either start to spit out free radicals and enzymes, or they just pop like a balloon]**
- Rupture of cells spills more glutamate into the area, and also perpetuates inflammation.

The complexity of this mechanism raises several questions about the best way to break the cycle of excitotoxicity to prevent further damage.

- Should we reduce the amount of glutamate?
- Block its release from glial cells?
- Bind or inactivate NMDA or AMPA receptors?

- Block the channels that let sodium and calcium into cells?
- Block the production or activity of digestive enzymes?
- And, importantly, can we do any of these in a way that does not interfere with normal glutamate signaling?