NASCIC
SCI RESEARCH
ADVOCACY COURSE

Module 6 – Neuroprotection

Summary of Key Points

This concludes Module 6: Neuroprotection. Before you take the quiz, let's review the key points from this module.

- The goal of "Neuroprotection" is to protect surviving neurons and axons after an SCI by stopping or reversing the biological processes that cause continued damage in the days to weeks after the initial injury.
- Neuroprotection includes drugs, medical devices, surgery, and other treatments that:
    - Restore blood flow
    - Relieve pressure
    - Reduce inflammation
    - Reduce free radicals and oxidants
    - Prevent glutamate excitotoxicity, or
    - Block apoptosis, a form of programmed cell death.
- Inflammation, free radicals, glutamate, and apoptosis are all necessary to maintain the body's health and functions, but rise to excessive levels after an SCI.
- Neuroprotection therapies must be able to restore balance by reducing their harmful effects without shutting down their necessary functions.

Let's also briefly review some of the key neuroprotection strategies we discussed.

- Immunomodulation involves manipulating immune cells so that they carry out their restorative functions but not their damaging inflammatory functions.
- Macrophages and neutrophils are cellular targets of immunomodulation.
- Methylprednisolone, minocycline, and G-CSF are examples of immunomodulatory drugs that are approved for other health conditions and may also be neuroprotective in SCI.
- Excitotoxicity is when excess glutamate overstimulates receptors on the cell membrane, causing the cells to fill with too much calcium and sodium, produce digestive enzymes, and die. Possible targets to prevent excitotoxicity include:

    - Glutamate itself;
    - The NMDA and AMPA receptors glutamate binds to;
    - The channels that let calcium and sodium in; and
    - The production or activity of the digestive enzymes that are released.
- Researchers are studying several ways to stop excess radicals from killing neurons by destroying cell membranes, proteins, and DNA. Experimental approaches include:
    - Antioxidant drug candidates that can neutralize excess radicals;
    - Targeting mitochondria by removing them, replacing them, or manipulating the way they function.
- Apoptosis is an orderly process of programmed cell death that is researchers hope to inhibit after SCI to protect uninjured neurons from dying.
    - There is more than one pathway that triggers apoptosis.
    - Enzymes in the caspase and calpain families are potential targets in these pathways.
    - Questions remain about which caspases or calpains to target, and how to do it safely.

Finally, let's revisit some important aspects of the methylprednisolone case study:

- The NASCIS 2 study of methylprednisolone did not answer how soon after injury methylprednisolone should be used because of several problems:
    - It missed its primary endpoint
    - The endpoint was not suitable for all the participants
    - It was unclear whether or how the endpoint related to functional recovery, or how meaningful it would be to people with an SCI
- Animal studies show better results when neuroprotection is administered soon after injury, but scientists don't know exactly how to translate time of treatment in animals to a similar time of treatment in people.
- In any case, in the real world treatment after an SCI is often delayed by several hours.
- In acute SCI, it is difficult to measure a treatment effect because:
    - Spinal shock can make the initial measurement of neurological function difficult

- Some people have spontaneous recovery, which is hard to distinguish from a treatment effect.

Now, let's take the quiz!