Neuroprotection

Author: SCIRE Community Team | *Reviewer: Chris S. Bailey* | *Published: 22 Jan 2018* | *Updated: ~*

"Neuroprotection" describes a wide range of treatments that aim to protect the spinal cord from further damage in the hours to weeks after an injury first happens. This page explains what neuroprotection is and outlines what the most promising treatments are right now.

Key points

- Spinal cord damage can worsen in the days to weeks after a spinal cord injury (SCI) because of processes like inflammation and lack of blood flow. This is called secondary injury.
- Neuroprotection is the use of medical treatments early after the initial injury to help protect the spinal cord from further damage.
- A wide range of medications has been suggested as neuroprotection, including the steroid methylprednisolone. Other types of treatments, such as cooling the body, have also been studied.
- Neuroprotection treatments are controversial at this time because there is not enough evidence to support using most treatments and there is disagreement amongst experts about how to interpret research findings for using methylprednisolone.
- Neuroprotection is an emerging area of research and many current studies are ongoing.

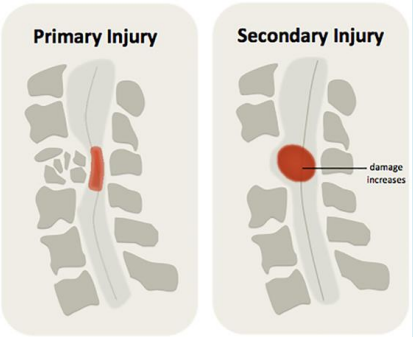
What is neuroprotection?

Neuroprotection is the use of medical treatments to protect the spinal cord from further injury in the hours to weeks after a spinal cord injury first happens. The term "neuroprotection" is used to describe a wide range of mainly experimental treatments that aim to reduce damage known as *secondary injury*.

Secondary injury

There are two main phases of damage that happen after a spinal cord injury, *primary injury* and *secondary injury*. The damage that is directly caused by the initial injury is called *primary injury*. Primary injury happens when the spinal cord is bruised, compressed, pulled or torn, which directly injures the nerve cells and spinal cord tissues.

As the body responds to the initial injury, several bodily processes can happen, which further damage the spinal cord. This is known as *secondary injury*. Secondary injury is caused by several processes, such as inflammation, lack of blood flow (ischemia), and build-up of damaging chemicals, which can worsen the original injury.



Secondary injury can worsen the spinal cord injury, expanding the size of the injury and leading to further loss of function.[1]

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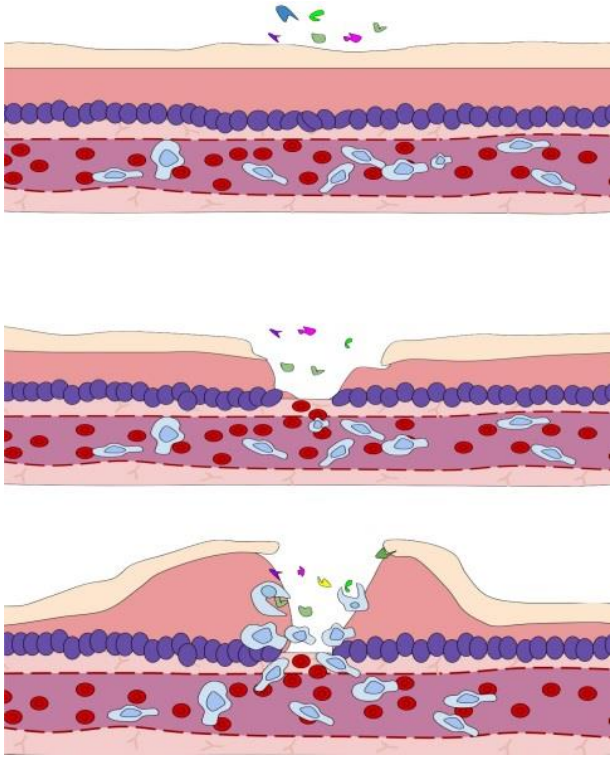
Secondary injury processes are responsible for expanding the size of the injury in the days to weeks afterwards and causing further loss of function. They can also make it harder for the body to heal.

Neuroprotection is intended to help protect the spinal cord from further damage, it is not intended to heal or repair already damaged tissues (this is called *regeneration*). Neuroprotective treatments are usually given as early as possible after injury, which is usually within the first 24 hours after injury or at the time of the first surgery.

Neuroprotection is also used to help protect against further nerve damage in other neurological conditions, such as brain injuries and degenerative diseases like amyotrophic lateral sclerosis (ALS).

What causes secondary injury?



During inflammation, special immune cells help get rid of foreign substances. This can lead to localized swelling.[2]

Inflammation and swelling

Inflammation is a natural bodily process where cells from the immune system (such as white blood cells) are brought to the site of an injury or illness. These cells remove harmful bacteria and dead cells from the area to help with healing.

Some inflammation is needed for healing. However, when it is excessive or continues for a long time, it can be damaging. Inflammation can end up breaking down healthy nerve cells (neurons), which makes the injury worse. Inflammation and other factors can also contribute to swelling of the spinal cord near the injury. Swelling can compress the spinal cord even more, damaging nerve cells and impairing blood flow.

Lack of blood flow

When the spinal cord is injured, the small blood vessels that provide oxygen and nutrients to the cord are also injured. If the blood vessels are torn, they may bleed within the spinal cord causing a bruise (called *haemorrhage*), which can increase the pressure on the spinal tissues and cause damage.

If the blood vessels are compressed or if there is not enough whole-body blood pressure (which happens as a part of neurogenic shock), they are also unable to maintain adequate blood flow to the cord. This is called *ischemia* (pronounced iss-kee-mee-ah). A lack of blood flow means that oxygen or nutrients cannot reach the tissues, which can damage or kill healthy cells. Ischemia can become severe within hours after the injury and can damage nerve cells and surrounding tissues, causing the injury to get bigger.

Build-up of damaging chemicals

Damaged nerve cells can cause the release of chemical compounds like glutamate. *Glutamate* is a neurotransmitter that stimulates nerve cells to fire. However, too much glutamate can overstimulate the cells, causing calcium to build up inside them, which damages and kills healthy cells. This is called *excitotoxicity.* Excitotoxicity is a major cause of secondary damage after SCI.

Inflammation, excitotoxicity and cell damage can release by-products called free radicals. *Free radicals* are molecules that are unstable and highly reactive. Free radicals can damage DNA, the fragile outer membranes, and other parts of cells.

Nerve cell death

Cells can die because of damage or injury (called *necrosis*) or because the body triggers the cells to self-destruct through a process called *apoptosis.* Apoptosis is sometimes called "programmed cell death" because it is a natural part of how the body gets rid of cells it doesn't need.

Under normal circumstances, apoptosis is carefully controlled by the body. However, certain conditions can trigger apoptosis when it is not needed. For example, damage to parts of the cell or chemical imbalances around or within the cell can trigger apoptosis.

After an SCI, secondary injury processes like excitotoxicity, inflammation, and the release of free radicals can trigger apoptosis. This can affect both nerve cells (neurons) and supporting cells like the cells that maintain myelin. This can even happen far away from the injury. Cell apoptosis after SCI expands the area of damage by killing previously healthy neurons and supporting cells.

What types of neuroprotection are there?

"Neuroprotection" refers to a wide range of different treatments, including medications and other treatments like cooling the body that aim to reduce secondary injury. It is sometimes used to describe surgical decompression and blood pressure control after SCI, although these treatments are not discussed on this page.

While there are many different neuroprotective treatment options being explored, below we briefly outline the most promising treatments currently being studied.

Most neuroprotection treatments are experimental

Currently, there are no widely accepted treatments used for neuroprotection. With the exception of methylprednisolone (see below), most of the potential treatments are currently being tested in research studies. Because of the experimental nature of these treatments, most of the treatments outlined below are not available for most people or used outside of research settings.

For details about the progress of ongoing clinical trials, please visit ClinicalTrials.gov.

Steroids (Methylprednisolone)

The steroid medication *Methylprednisolone* is the most well-known neuroprotective treatment. It is also the only treatment that is currently used outside of research studies. High doses of methylprednisolone

may affect many different aspects of secondary injury, including reducing inflammation and damage from free radicals that are thought to help prevent cells from dying after injury.

Three large-scale clinical trials were completed during 1980s and 1990s, which established methylprednisolone as a standard treatment that all patients with SCI should receive. However, later debate among experts criticized conclusions made in these studies and questioned the value of methylprednisolone as a treatment. It has been argued that methylprednisolone has shown only limited benefits for recovery, but well-established risk of side effects like infections.

Refer to SCIRE Professional's page on Steroids for more information!

At this time, methylprednisolone continues to be a controversial treatment among experts. It may be used in some clinical settings in certain groups of people with SCI.

Riluzole

Riluzole is a drug that blocks sodium from entering into nerve cells, which may help to reduce excitotoxicity. Riluzole is currently used to treat the degenerative neurological condition amyotrophic lateral sclerosis (ALS).

Animal studies have shown that Riluzole is effective as a neuroprotection treatment in rats with SCI. One preliminary study supported that Riluzole is safe and has potential to provide neuroprotection after SCI in humans. Currently, a large-scale clinical trial is in progress to determine whether Riluzole is effective as neuroprotection after SCI.

Minocycline

Minocycline is an antibiotic medication that is most commonly used to treat bacterial infections. Minocycline may also have neuroprotective effects after SCI. Animal studies have shown that minocycline may suppress immune cells involved in inflammation, cell death and the release of damaging chemicals. An early clinical trial has shown that IV minocycline is safe for use after acute SCI, and has potential as neuroprotection in people with incomplete SCI. Currently, a large-scale study is ongoing to investigate whether minocycline is effective as neuroprotection after SCI.

Cooling the body (therapeutic hypothermia)

Cooling the body, known as *therapeutic hypothermia*, is a treatment that involves reducing the temperature of the body to help protect against further damage. The body is cooled by inserting a cooling catheter into a blood vessel, which cools blood moving through circulation by a few degrees. Reducing body temperature slows metabolism, which can reduce inflammation and minimize further damage. This procedure is currently used to help prevent neurological damage after cardiac arrest.

A small preliminary study has shown that therapeutic hypothermia is safe and has potential as neuroprotection after SCI. Currently, a clinical trial is underway to determine whether spinal cord cooling is effective as neuroprotection for SCI in humans.

Cerebrospinal fluid drainage

Cerebrospinal fluid (*CSF*) *drainage* is a technique that involves inserting a small catheter through the coverings of the spinal cord to drain a small amount of the fluid that surrounds the spinal cord and brain (called *cerebrospinal fluid*). Draining the cerebrospinal fluid is thought to help relieve pressure and reduce further injury to the spinal cord.

Animal studies have shown that cerebrospinal fluid drainage may help improve spinal cord blood flow when combined with careful blood pressure management. One small research study has shown that cerebrospinal fluid drainage was safe for use in people with acute SCI. A larger study has been completed to determine whether cerebrospinal fluid drainage is effective as neuroprotection after SCI. However, the results have not yet been published.

Magnesium

Magnesium has been proposed as a neuroprotective treatment because it can help to reduce excitotoxicity and inflammation. Animal studies have shown benefits for magnesium as neuroprotection.

Cethrin (VX-210)

Cethrin (*VX-210*) is a medication that reduces the effects of *Rho*, a protein that is present in inflammation. Rho causes damage to nerve cells and prevents nerve cell regrowth. Cethrin reverses the action of Rho, which may help protect nerve cells and allow neurons to regrow. An early study has shown that Cethrin is safe. A clinical trial testing whether it is effective has been completed with the results pending publication.

Other treatments being studied

A wide range of other treatments have been or are currently being studied. These include:

- Fibroblast growth factor
- Hepatocyte growth factor
- Erythropoetin (EPO)
- GM-1 Ganglioside (Sygen)
- Granulocyte-colony stimulating factor (G-CSF)
- Thyrotropin-releasing hormone (TRH)
- Glibenclamide or glyburide
- Special diets such as intermittent fasting

Neuroprotective treatments that are not effective

Research evidence on the following treatments has suggested that they are not effective for use as neuroprotection after SCI. These include:

- Naloxone
- Tirilazad mesylate (was not more effective than methylprednisolone, but had more side effects)
- Nimodipine
- Gacyclidine

Refer to SCIRE Professional's module on Neuroprotection for more information!

Why is it so difficult to find effective neuroprotective treatments?

Secondary injury is a complicated process that scientists are still working to understand. While there are many promising treatments currently being studied, there are no widely accepted treatments so far. Neuroprotection is a relatively new area of study compared to other aspects of medicine and there are a number of other factors that makes neuroprotection difficult to study.

Testing experimental treatments is lengthy and expensive

Most neuroprotective treatments are experimental and have not been tested in humans. This means that each treatment must undergo vigorous testing to determine if it is safe and effective. There are several phases of study that must be done. Usually, research studies are tested on animals first, and then typically go through at least three phases of human studies (*Phase I, II, and III clinical trials*) before a treatment can be determined to be safe and effective for real world use. These trials can cost millions of dollars and take several years to complete.

Designing and conducting high quality studies is very difficult

It is also very difficult to design and carry out high quality studies. There are many factors relevant to the design and how the study findings are analyzed that can affect the study's findings. This is why many previous research studies (such as those done on methylprednisolone), are controversial even amongst experts.

In addition, neuroprotection treatments are usually given immediately after the injury during a highly stressful and confusing period. It can be challenging for patients and their families to determine whether they want to take part in a study and give their consent to participate.

Promising experimental treatments often do not translate into effective treatments

Unfortunately, many treatments that are shown to be effective in animal studies do not go on to show the same effects in the real-world scenarios involved in clinical trials. Translating research into effective treatments is a complex process with many steps that are undertaken to ensure that treatments are safe and effective.

Because secondary injury is so complex, some researchers believe that it is unlikely that one single treatment will be discovered that will completely protect the spinal cord from further damage. Research may lead clinicians to several different treatment options that may be used together or in different situations to help protect the spinal cord from further damage.

The bottom line

Neuroprotection is the use of medical treatments early after the initial injury to help protect the spinal cord from further damage caused by secondary injury.

There are many different treatments being studied for use as neuroprotection. The steroid methylprednisolone is the most well-known treatment, but its use is controversial among experts. Most neuroprotective treatments are currently being investigated in research studies.

Neuroprotection after SCI is an emerging area of research and clinical care that we will learn more about as research findings come to light in the next few years.

Related resources

Want to learn more about current neuroprotection clinical trials? Search for studies on https://clinicaltrials.gov/

Abbreviated reference list

Parts of this page have been adapted from the SCIRE Professional "Neuroprotection During the Acute Phase of Spinal Cord Injury" Module:

Mullen E, Mirkowski M, Hsieh JTC, Bailey C, McIntyre A, Teasell RW. (2015). Neuroprotection during the Acute Phase of Spinal Cord Injury. In Eng JJ, Teasell RW, Miller WC, Wolfe DL, Townson AF, Hsieh JTC, Connolly SJ, Noonan VK, Loh E, McIntyre A, editors. Spinal Cord Injury Research Evidence. Version 5.0: p 1-42. Available from: scireproject.com/evidence/neuroprotection-acute-phase/methods/

Full reference list available from: community.scireproject.com/topic/neuroprotection/#reference-list
Glossary terms available from: community.scireproject.com/topics/glossary/

Image credits

1. 'Figure 3 - There are two phases of injury after damage to the spinal cord' from: O'Higgins M, Badner A and Fehlings M (2017) What Is Spinal Cord Injury? Front Young Minds. 5:17. doi: 10.3389/frym.2017.00017. (CC BY 3.0)
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