May 11, 2021

Neurobiology

How to counteract age when the nervous system is damaged

by Nathan J. Michaels[1] | Postdoctoral Research Fellow; Jason R. Plemel[1] | Assistant Professor

doi.org/10.25250/thescbr.brk531

[1]: Department of Medicine, Division of Neurology, University of Alberta, Edmonton, Canada

This Break was edited by Ayala Sela, Associate Editor - TheScienceBreaker

For most neurological disorders, age means more damage and worse clinical outcomes. Using advanced techniques, we determined what it is about the aging central nervous system that makes it more susceptible to damage. We then targeted the source of this damage with a medication never before used in the brain and spinal cord.

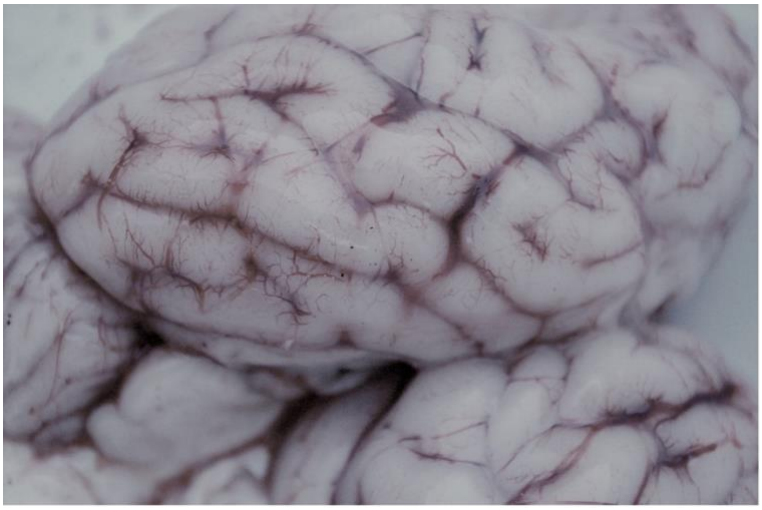

Image credits: ennaziz – Pixabay

As we get older, the body becomes more prone to damage and is less able to repair it. The delicate tissue of the brain and spinal cord (collectively referred to as the central nervous system) are no exception. With age, damage due to traumatic brain injury, spinal cord injury, or stroke is more widespread and patients with multiple sclerosis are more likely to experience steady neurological decline.

We aimed to determine what it is about aging that makes damage in the central nervous system more detrimental. We focused on two structures critical for transmitting information: nerve fibers and myelin.

The nerve fiber - or axon - is a long, thin extension protruding from the body of the neuron. Much like an electrical cable carries electricity from one point to another - the wall socket to a lamp, for example - the nerve fiber carries electrical impulses from one neuron to the next. Normally, hundreds of nerve fibers are aligned in tracts connecting brain regions to each other and to different parts of the body. Within the tract, nerve fibers are individually wrapped by a fatty substance called myelin in tight, concentric circles. When nerve fibers are injured, the myelin can unravel, degrade and disappear. The nerve fibers can also be “cut”, each end retracting away from the site of injury (which is also called a lesion). When we looked at lesions that formed at an older age, we saw fewer nerve fibers and more myelin beginning to unravel compared to lesions

formed at a younger age. Fewer nerve fibers mean more have been "cut" and more unraveled myelin means it has been harmed in some way. Both of these indicators suggest more damage occurs in lesions formed at an older age. To better understand why, we looked at mRNA.

Strands of mRNA serve as building instructions for proteins. Proteins dictate how cells function, interact with one another and affect their environment. Using mRNA to infer the amounts and function of proteins is like using the blueprints of a building to visualize what the building looks like and what it might be used for. You can't know for sure, because you can't see the building itself, but the blueprints allow you to make an educated guess. By analyzing protein building instructions, we could make out how cells in the lesions function and interact with one another.

We found that cells in lesions formed at an old age were producing more reactive oxygen species - small molecules that, left unchecked, damage the essential building blocks of cells. If the damage is extensive enough, cells die, potentially disrupting the tissue and organ. Inside the brain, these reactive oxygen species are produced by special immune cells, called macrophages, that "eat" invaders. These immune cells generate the damaging molecules to kill invading microbes and break down the eaten foes.

In lesions like those we were studying, two types of macrophages can be found: those formed from immune cells already inside the central nervous system; and another typed formed from immune cells in the blood that enter the central nervous system when it has been injured.

We were able to visually label each type of immune cell. This allowed us to look under a microscope and determine whether the macrophages most responsible for generating reactive oxygen species came from inside or outside the central nervous system. Distinguishing between the two cell types may seem trivial, but it has important implications for treatment. The brain and spinal cord are isolated behind a largely impermeable structure called the blood-brain barrier, which isolates the central nervous system from the rest of the body. If immune cells within the central nervous system are the main producers of reactive oxygen species, drugs must be capable of crossing the blood-brain barrier to influence their activity. If the immune cells coming from outside the central nervous system are the culprit, drugs could target these cells before they cross into the brain and spinal cord tissue. After looking at thousands of cells, we found the immune cells within the brain and spinal cord were the main source of reactive oxygen species in lesions formed at an older age. This means these cells should be targeted in order to stymy their toxicity.

We targeted reactive oxygen species production in the brain and spinal cord with a drug called indapamide. This is a drug normally used to treat hypertension and has never been used to target damage in the central nervous system. We identified it as a candidate in a previous study where hundreds of generic drugs were screened for their ability to counteract reactive oxygen species and cross the blood brain barrier into the central nervous system. After treatment with indapamide, we saw less loss of nerve fibers and a greater preservation of myelin in the old age lesions. Something about the drug makes injury in these lesions less detrimental.

Our current studies focus on determining exactly how indapamide works: does it just interact with and neutralize reactive oxygen species? Or does it act directly on cells to prevent them from producing reactive oxygen species in the first place? We also need to determine how much of the drug is optimal. Knowing some of the factors that makes injury in the brain and spinal cord worse with age—and how to

target those factors—will make treatments for neurological conditions such as multiple sclerosis, traumatic brain and spinal cord injury and stroke much more effective. And it will help protect our increasingly aged population from unnecessary debilitation.