Neuropathic Pain:
Are You Too Sensitive?

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Introduction

We're all familiar with the sudden shock we feel when we hurt ourselves, whether it is the discomfort of a paper cut or the teeth-gritting pain of a broken bone. But why do we have mechanisms to feel pain at all? It seems counterintuitive that pain is beneficial, but, in fact, pain warns us of actual or potential damage to tissue, allowing us to quickly respond to dangerous situations. Sensory neurons transmit touch and pain stimuli to the spinal cord; from there, the signals are sent to the sensory cortex in the brain. If these sensory pathways are damaged, not only do we lose a critical self-protection mechanism but the neurons can also become dysfunctional and a condition known as **neuropathic pain** can develop.

KEY CONCEPTS

- Sensory neurons transmit pain information to the central nervous system.
- Damage to pain pathways can result in long-term pathological changes in neurons.

Neuropathic pain has no simple definition, and it is used as a catch-all term to describe a state of chronic pain that can arise when neurons have been damaged because of amputation, cancer, direct injury to the spinal cord or peripheral nerves, or pathologies related to diabetes or human immunodeficiency virus (HIV). Neuropathic pain is characterized by the development of **allodynia** of the sensory pathways. Allodynia is sensitization to a stimulus that would not normally be painful but now is, making even a light summer breeze or the softest touch of clothing against the skin seem excruciating.

Between 2 and 3 percent of Canadians experience neuropathic pain. It is a devastating condition that can reduce people's quality of life. Over-the-counter pain medications are largely ineffective in alleviating symptoms. Currently, researchers are trying to identify the underlying causes of neuropathic pain, with the hope that more effective treatments can be developed. Scientists from Laval and McGill Universities in Quebec have collaborated to investigate the cellular mechanisms through which neuronal hypersensitivity develops after injury.

Research Question
How does injury lead to neuronal hypersensitivity and allodynia?

Surprisingly, the secret may lie not in the neurons at all but in a type of neuroimmune cell found throughout the central nervous system (CNS)—namely, microglial cells (see Photo A). **Microglia** are a type of glial cell. Glial cells are a family of non-neuronal cells in the CNS that modulate neuronal signalling and support and protect neurons. Specifically, microglia are immune cells that patrol the CNS and become activated in response to invading pathogens, stress, and damaged tissue. Once activated, they release

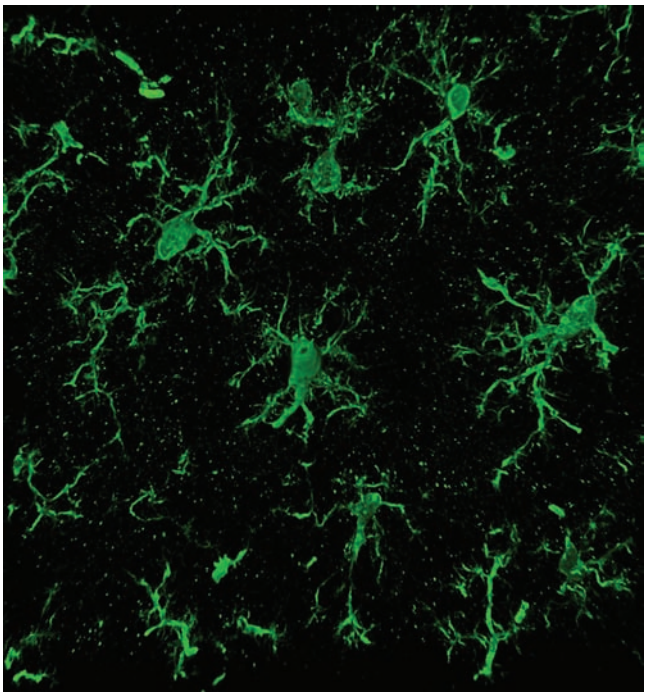

PHOTO A. Microglia in the brain.
Microglia are neuroimmune cells in the CNS. They extend and retract their processes, and they scour the CNS for invading pathogens or damaged tissue.
Source: Photo by Cheryl Sank, University of Calgary.

signalling molecules, including growth factors. One such growth factor is **brain-derived neurotrophic factor (BDNF)**. BDNF initiates multiple biochemical pathways, some of which alter the activity levels of neurons, making them fire more or less often. The release of BDNF may be an underlying cause of the changes that take place following injury to neurons.

Hypothesis

In response to neuronal damage, microglia release signalling molecules (BDNF) that increase the excitability of sensory neurons in the spinal cord and lead to allodynia.

Methods and Results

With rats as a model system, a team led by Yves De Koninck at Laval University used a combination of behavioural tests and electrical recordings from sensory neurons in the rat spinal cord to explore this hypothesis.

To assess the sensitivity of the touch pathways, the researchers measured the paw-withdrawal reflex. Following stimulation of the rat's paw, they measured how quickly the rat would pull its paw away and compared the withdrawal times before and after the spinal cord had been damaged. The spinal cord was damaged by placing a compression cuff around the cord to cause a crushing injury. If the rat withdrew its paw faster after injury, it likely meant that the sensitivity of the pathway had increased and that the rat perceived the stimulus as more uncomfortable, an example of allodynia. As expected, rats did display a faster withdrawal reflex (i.e., they pulled back faster) after spinal cord injury than before, which indicated that the sensory pathways had become hypersensitive.

Next, the researchers asked whether the application of either microglia or BDNF could lead to hypersensitivity when the spinal cord was intact. To assess this, activated microglia or BDNF were injected into the spinal cords of healthy rats, and again the withdrawal reflex was measured. Both manipulations initiated a more sensitive

TABLE 1. Summary of Experiments

Experiment	Spinal Cord	Microglia	BDNF Present	Neuronal Excitability	Paw Withdrawal Reflex
Control	No damage	Inactive	No	Normal	Normal
Activated microglia added	No damage	Active	Yes	Increased	Sensitized
BDNF added	No damage	Inactive	Yes	Increased	Sensitized
Spinal cord injury	Damaged	Active	Yes	Increased	Sensitized

paw withdrawal. Thus, the in vivo manipulations of direct injury, the injection of activated microglia, and the injection of BDNF all sensitized the system and elicited allodynia.

Was this sensitization the result of a change in the spinal cord neurons themselves or a change in the way the brain integrates sensory information? A technique called electrophysiology was used to answer this question. With this technique, researchers can make direct electrical recordings from spinal cord neurons and measure how excitable the neurons are. Exposing the spinal cord neurons to (1) activated microglia or (2) BDNF made the neurons more excitable. These effects were blocked when pharmacological inhibitors that prevent microglia from becoming activated or prevent BDNF from interacting with its membrane-bound receptor were used. These experiments demonstrated that it was the direct effect of BDNF released from activated microglia on spinal cord neurons that caused allodynia of the paw-withdrawal response and increased the excitability of the neurons. These experiments are summarized in Table 1.

Conclusions

The results from these experiments tell us that an injury to the spinal cord activates microglia, causing these cells to release the signalling molecule BDNF, which triggers the spinal cord neurons to become more excitable. The hypersensitivity of the sensory pathway may lead to the development of neuropathic pain symptoms, such as allodynia. This cellular pathway is summarized in Figure 1.

Future Directions

The future lies in identifying which steps in the cellular pathway are the most susceptible to clinical interventions that will be safe for people. Because the treatments available in Canada involve a long list of prescription medications, each with substantial side effects, the most promising course of action may be to prevent neuropathic pain before it develops. As more is discovered about the link between nerve damage and the development of hypersensitivity, more potential targets for medication may be found, helping people to effectively manage this painful condition.

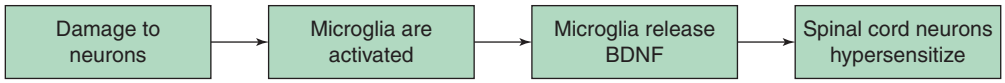

FIGURE 1. Cellular pathway in the development of neuropathic pain.

Critical Thinking Questions

1. Why is the ability to sense pain actually a good thing?
2. Why were microglia identified by the researchers as a potential target for a role in the development of neuropathic pain?
3. How did the researchers examine changes in the sensitivity of pain-sensing pathways?

Further Research Question

What are some of the current techniques used to address neuropathic pain in people?

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