

NEW CULPRITS IN CHRONIC PAIN

KEY CONCEPTS

- Chronic pain that persists after an injury heals is often caused by overly excited pain-sensing neurons that signal without an external stimulus.
- Traditional pain drugs that target neural cells directly rarely quiet these abnormal pain messages because the neurons' heightened sensitivity is driven by a different type of cell called glia.
- Such cells monitor the activity of neurons and attempt to keep them healthy and functioning efficiently. But well-intentioned glial reactions to intense pain can at times prolong that pain.

—The Editors

Glia are nervous system caretakers whose nurturing can go too far. Taming them holds promise for alleviating pain that current medications cannot ease

BY R. DOUGLAS FIELDS

Helen's left foot slipped off the clutch on impact, twisting her ankle against the car's floorboard. It felt like a minor sprain at the time, she recalls, but the pain never subsided. Instead it intensified. Eventually, the slightest touch, even the gentle brush of bed linen, shot electric flames up her leg. "I was in so much pain I could not speak, yet inside I was screaming," wrote the young Englishwoman in an online journal of the mysterious condition that would torment her for the next three years.

The chronic pain suffered by people like Helen is different from the warning slap of acute pain. Acute pain is the body's most alarming, intense sensation, whose purpose is to stop us from further injuring ourselves. This type of pain is

also called pathological pain because an external cause, such as tissue damage, produces the signals that travel the nervous system to the brain, where they are perceived as pain. But imagine if the gut-wrenching agony of a real injury never stopped, even after the wound healed, or if everyday sensations became excruciating: "I was unable to shower ... the water felt like daggers," Helen remembers. "The vibrations in a car, someone walking across floorboards, people talking, a gentle breeze ... would set off the uncontrollable pain. Common painkillers ... even morphine had no effect. It was like my mind was playing tricks on me."

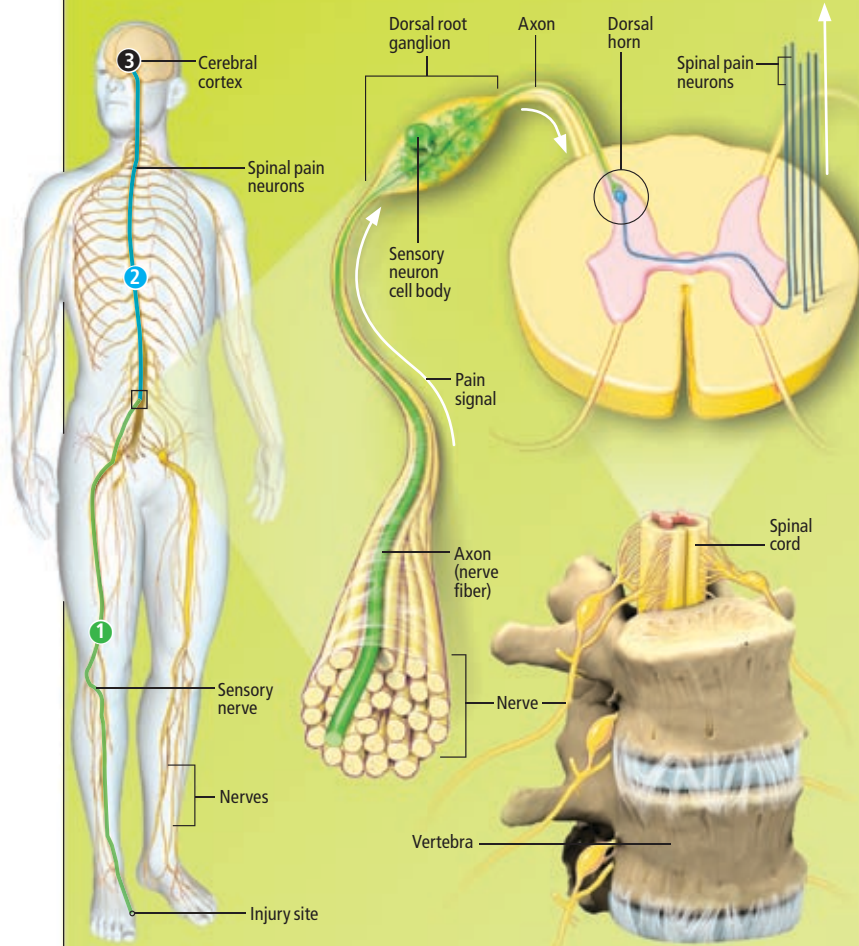
Unfortunately, Helen was right. Her chronic pain stemmed from a malfunction in the body's pain circuits, causing them to continually trig-

GERALD SLOTA



PAIN CIRCUITRY

Sensations from an injured part of the body travel through three stages of neural circuitry before being perceived as pain by the brain. At the relay point in the spine where messages are passed from the first stage to the next, support cells called glia monitor and regulate the behavior of neurons to ease the transmission of signals.

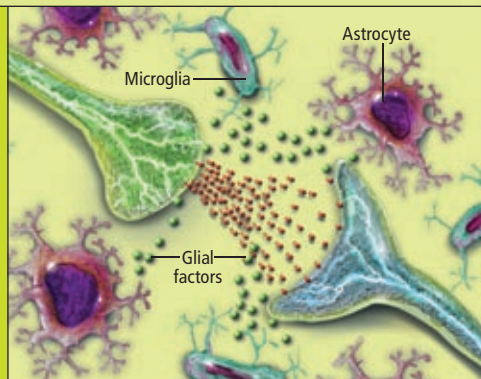


▲ PAIN SENSATION

After an injury, such as breaking a toe, sensory nerves ① responsible for detecting noxious stimuli carry the signals from the leg to the dorsal horn of the spinal cord. Inside the spinal cord those peripheral sensory nerve fibers relay their messages to dedicated pain-transmitting neurons that carry the signals up the spinal cord to the base of the brain ②. When the signals reach the cerebral cortex ③, they are perceived as pain.

EAVESDROPPERS CHIME IN ▶

Neurons are surrounded by astrocytes and microglia, helper cells that provide nourishment and protection. Collectively known as glia, these support cells also monitor and regulate neural activity by contributing sensitizing or dampening factors as needed to sustain neural signaling.



ger a false alarm, one that is termed neuropathic because it arises from the misbehavior of the nerves themselves. When the false signals reach the brain, the agony they inflict is as real as any life-threatening pain, yet it never goes away and doctors are often powerless to quiet it.

Recent research is finally elucidating why traditional pain drugs often fail to quell neuropathic pain: the drugs target only neurons when the underlying source of the pain can be the dysfunction of nonneuronal cells called glia that reside in the brain and spinal cord. New insights into how these cells, whose job is to nurture the activity of neurons, can themselves become unbalanced and disrupt neuronal function are sparking new ideas for treating chronic pain. The work is also providing a surprising perspective on an unfortunate corollary of current pain treatment in some people: narcotic addiction.

Pain Circuits and Breakers

Understanding what could cause pain to persist after an injury has healed requires some knowledge of what causes pain at all. Although the sensation of hurt is ultimately perceived in the brain, the nerve cells that produce it are not located there; rather they line the spinal cord, gathering sensory information from throughout the body. Dorsal root ganglion (DRG) neurons, which represent the first stage of a three-part pain-sensing circuit, have their cell bodies stuffed like clusters of grapes in the seam between each vertebra of the backbone, resembling rows of buttons on a double-breasted jacket running from tailbone to skull. Each DRG neuron, like a person with two outstretched arms, extends one slender feeler, known as an axon or fiber, outward to survey a tiny distant region of the body while reaching its other axon into the spinal cord to touch a neuron that will relay impulses through the second stage in pain circuitry, a chain of spinal cord neurons. These spinal pain-transmitting cells in the cord relay messages from DRG neurons up to the final stage, the brain stem and ultimately the cerebral cortex. Pain signals originating from the left side of the body cross inside the spinal cord to travel to the right brain, and signals from the right side are sent to the left brain.

Interrupting the flow of information at any point along the three-stage pain circuit can blunt acute pain. Local anesthetics, such as the Novocain dentists use to painlessly extract a tooth, numb axon tips around the injection site, preventing the cells from firing electrical impulses.

A “spinal block,” often used to eliminate pain in childbirth, stops pain impulses at the second stage of the circuit, as bundles of DRG cell axons enter the spinal cord to meet spinal neurons. This blockade leaves the mother fully conscious to experience and assist in the painless delivery of her child. A morphine injection works at the same location, reducing transmission of pain signals by spinal neurons while leaving awareness of nonpainful sensations intact. In contrast, general anesthetics used in major surgery disrupt information processing in the cerebral cortex, rendering the patient completely unaware of any sensory input from neural pathways outside the brain.

Our body’s natural painkillers work at these same three links in the pain circuit. A soldier charged with adrenalin in battle may suffer grievous injury while unaware of the wound because the cerebral cortex ignores the pain signals while dealing with a highly emotional and life-threatening situation. In natural childbirth, a woman’s body releases small proteins called endorphins that dampen the transmission of pain signals as they enter her spinal cord.

Hormones, emotional states and numerous other factors can also dramatically alter a person’s perception of pain by modulating the transmission of messages along pain pathways. In addition, many biological processes and substances that alter the ebb and flow of molecules through ion channels in individual nerve cells all contribute to regulating the sensitivity of nerves themselves. When an injury occurs, these factors can ease controls on neuronal firing, thereby facilitating the neurons’ job of transmitting pain signals.

That uninhibited state, however, can last too long, leaving DRG cells hypersensitized and causing them to fire pain messages without an external stimulus. This situation is the primary cause of neuropathic pain. The increased neural sensitivity can also cause abnormal feelings of tingling, burning, tickling and numbness (paresthesia) or, as in Helen’s experience of the shower of daggers, can amplify light touch or temperature sensations to painful levels (allodynia).

Efforts to understand how neurons in the pain circuitry become hypersensitive after injury have, not surprisingly, long focused on what goes wrong in neurons—work that has yielded some clues but not a complete picture. My own research and that of many colleagues have demonstrated, for instance, that the very act of firing impulses to send pain signals alters the activity

THE AUTHOR



R. Douglas Fields is editor in chief of the journal *Neuron Glia Biology* and has written several articles on neuroscience topics for *Scientific American*, most recently in March 2008 about the role of white matter in the brain. His forthcoming book, *The Other Brain* (Simon & Schuster), describes new insights into how glia regulate brain functions in health and disease.

GLOSSARY

NEUROPATHIC PAIN

Persistent pain that develops after nerve damage caused by injury. Can include unpleasant sensations, numbing, burning, prickling, heat, cold and swelling. Other causes of nerve damage that leads to neuropathic pain include viral infection of nerves, diabetic damage to peripheral nerves, or nerve injury resulting from cancer-related surgery, chemotherapy or nutritional deficits.

ALLODYNIA

Perception of nonpainful touch or temperature stimuli as painful.

HYPERALGESIA

Increased sensitivity to painful stimuli.

HYPERESTHESIA

Increased sensitivity to stimulation (hyperalgesia plus allodynia).

PARATHESIA

Abnormal sensation, such as burning, in response to touch.

of genes inside pain neurons. Some genes regulated by neuronal firing encode the ion channels and other substances that heighten the cells’ sensitivity. The intense activation of DRG cells when tissue is injured can thus cause the kinds of sensitizing changes in those neurons that might result in neuropathic pain later on. Our studies and the work of other laboratories also reveal, however, that neurons are not the only cells responding to painful injury and releasing the substances that promote neural sensitivity.

Glia far outnumber neurons in the spinal cord and brain. They do not fire electrical impulses, as neurons do, but they have some interesting and important properties that influence neuronal firing. Glia maintain the chemical environment surrounding neurons: beyond delivering the energy that sustains the nerve cells, they sop up the neurotransmitters that neurons release when they fire an impulse to a neighboring neuron. Sometimes glia even dispense neurotransmitters to augment or modulate the transmission of neuronal signals. When neurons are injured, glia release growth factors that promote neural survival and healing, and they release substances that call on cells in the immune system to fight infection and initiate healing. And yet recent research is revealing that these activities on the part of glia, to nurture neurons and facilitate their activities, can also prolong the state of neural sensitization.

Glia Become Suspect

For more than a century scientists have known that glia respond to injury. In Germany in 1894 Franz Nissl noticed that after a nerve is damaged, glial cells at the spots where nerve fibers connect in the spinal cord or brain change dramatically. Microglia become more abundant, and a larger type, called astrocytes because of their star-shaped cell bodies, becomes much beefier, plumped up with thick bundles of filamentous fibers that fortify its cellular skeleton.

These glial responses were commonly understood to promote nerve repair after injury, but how they did so was unclear. Furthermore, if an injury—such as a twisted ankle—is inflicted far from the spinal pain circuitry, the astrocytes in the spine must be responding not to direct injury but rather to changes in signaling at the relay point between DRG and spinal neurons. This observation implied that astrocytes and microglia were monitoring the physiological properties of pain neurons.

Over the past two decades glia have been

TOO MUCH OF A GOOD THING

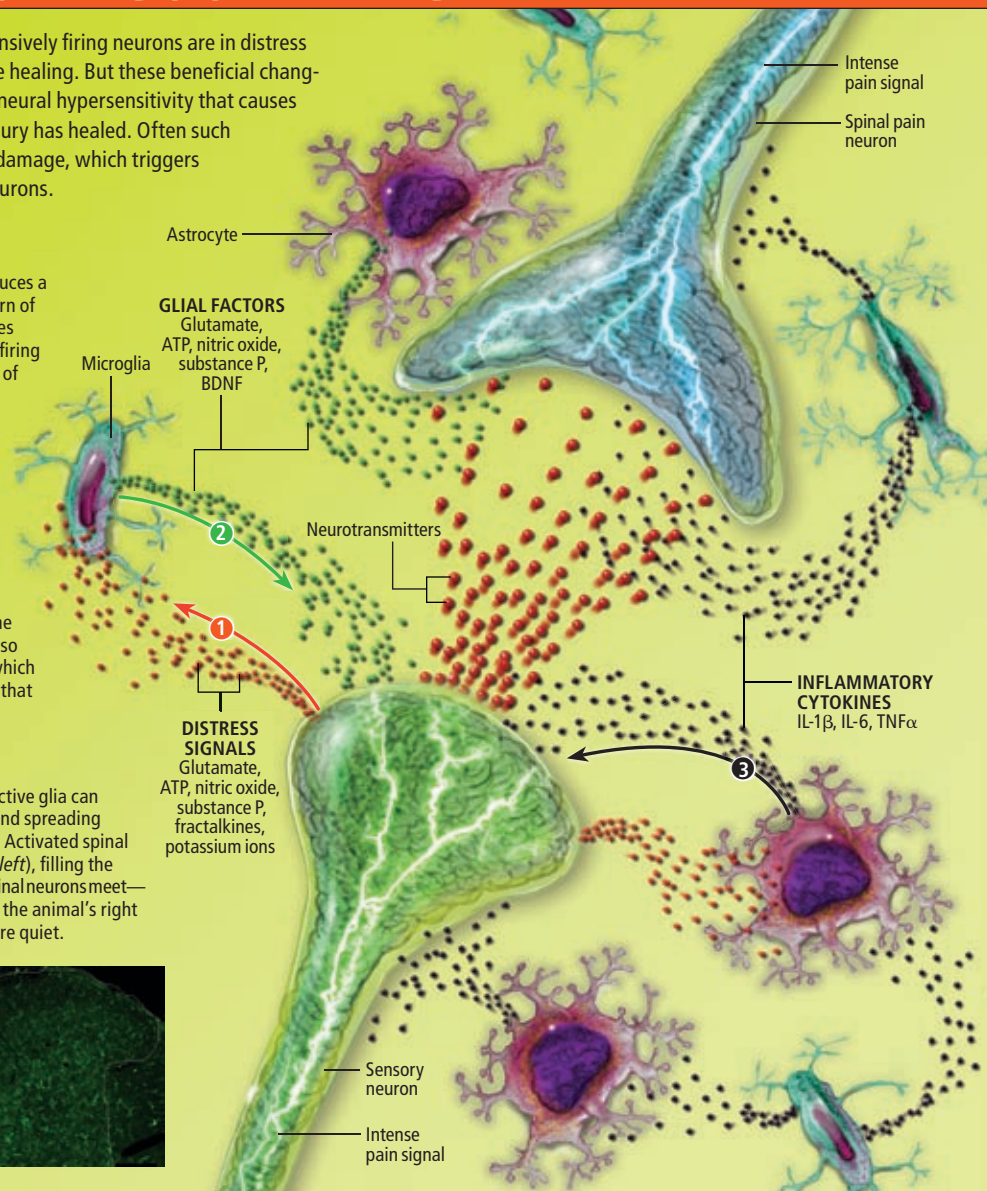
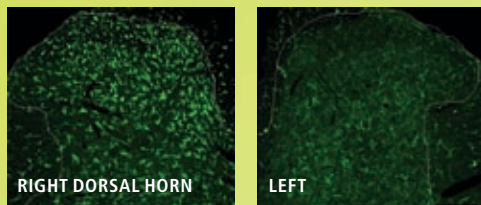
After an injury, glia sensing that intensively firing neurons are in distress react to restore balance and promote healing. But these beneficial changes, if prolonged, can lead to chronic neural hypersensitivity that causes pain to continue after the original injury has healed. Often such neuropathic pain begins with nerve damage, which triggers glial responses that further excite neurons.

GLIA ACTIVATION ▶

An injury that damages nerve fibers produces a barrage of pain signaling in the dorsal horn of the spine, where peripheral sensory nerves meet spinal pain neurons. An intensively firing sensory neuron generates large amounts of neurotransmitters as well as other molecules that glia interpret as signs of distress **1**, sending the helper cells into a reactive state. Glia normally mop up excess neurotransmitters, but reactive glia reduce their neurotransmitter uptake and begin producing molecules intended to stabilize and heal the neurons **2**. These glial factors act to either reduce inhibitory forces on neurons or to stimulate them, allowing the cells to fire more easily. Neural distress also causes the glia to release cytokines **3**, which induce inflammation, a healing response that also further sensitizes neurons.

GLIA-SUSTAINING PAIN

Excitatory/inflammatory signaling by reactive glia can activate neighboring glia, perpetuating and spreading neural hypersensitivity in the spinal cord. Activated spinal astroglia are visible below (*bright green, left*), filling the right dorsal horn of a rat—where DRG and spinal neurons meet—10 days after injury to the sciatic nerve in the animal's right leg. Glia on the left (*image below right*) are quiet.



shown to possess many mechanisms for detecting electrical activity in neurons, including channels for sensing potassium and other ions released by neurons firing electrical impulses and surface receptors for sensing the same neurotransmitters that neurons use to communicate across synapses. Glutamate, ATP and nitric oxide are among the significant neurotransmitters released by neurons that are detected by glia, but many others exist. This array of sensors allows glia to survey electrical activity in neuronal circuits throughout the body and brain and to respond to changing physiological conditions [see “The Other Half of the Brain,” by R. Douglas Fields; *SCIENTIFIC AMERICAN*, April 2004].

Once scientists recognized the breadth of glial responses to neural activity, attention returned to the support cells’ suspicious behavior at pain-relay points. If glia were monitoring neural pain transmissions, were they affecting them, too? Exactly 100 years after Nissl’s observation of glia responding to nerve injury, a simple experiment first tested the hypothesis that glia might participate in the development of chronic pain. In 1994 Stephen T. Meller and his colleagues at the University of Iowa injected rats with a toxin that selectively kills astrocytes, then assessed whether the animals’ sensitivity to painful stimulation was reduced. It was not, showing that astrocytes have no ob-

Boulder and her colleagues have shown in animals that using an experimental compound to block a particular TLR subtype, TLR-4, on glial cells in the spinal cord reversed neuropathic pain that stemmed from damage to the sciatic nerve. Interestingly, naloxone—a drug used to blunt the effects of opiates in addiction treatment, also blocks glial responses to TLR-4 activation. Watkins has demonstrated in rats that naloxone can reverse fully developed neuropathic pain.

Another existing drug, indeed an ancient pain-relieving substance that can work when many others fail, is marijuana, which has been legalized for medicinal use in some states. Substances in the marijuana plant mimic natural compounds in the brain called cannabinoids, which activate certain receptors on neurons and regulate neural signal transmission.

Two types of cannabinoid receptor occur in the brain and nervous system, however: CB1 and CB2. They have different functions. Activating the CB2 receptor brings pain relief, whereas activating CB1 receptors induces the psychoactive effects of marijuana. Remarkably, the CB2 receptor that relieves pain does not appear on pain

neurons; it is on glia. When cannabinoids bind to microglial CB2 receptors, the cells reduce their inflammatory signaling. Recent studies have found that as chronic pain develops, the number of CB2 receptors on microglia increase, a sign that the cells are valiantly trying to capture more cannabinoids in their vicinity to provide analgesic relief. Now pharmaceutical companies are vigorously pursuing drugs that can be used to control pain by acting on glial CB2 receptors without making people high.

Blocking inflammatory cytokines with existing anti-inflammatory medicines, such as anakinra (Kineret) and etanercept (Enbrel), has also reduced neuropathic pain in animal models. In addition to stemming inflammatory signals, several groups have demonstrated that adding anti-inflammatory cytokines, such as interleukin-10 and IL-2, can subdue neuropathic pain in animals. Two existing drugs, pentoxifylline and AV411, both inhibit inflammation by stimulating cells to produce IL-10. Moreover, assorted research groups have reversed neuropathic pain for up to four weeks by delivering the genes that give rise to IL-10 and IL-2 into the muscles or the spine of animals.

A few of these drugs have entered human trials for pain [see table on opposite page], including AV411, which is already used as an anti-inflammatory treatment for stroke in Japan. A trial in Australia showed that pain patients voluntarily reduced their dosages of morphine while on the drug, a sign that AV411 was contributing to relieving their pain. But AV411 may be working by mechanisms that go beyond calming pain caused by inflammation, highlighting a surprising twist in the tale of glia and pain.

Restoring Balance

Morphine is among the most potent painkillers known, but doctors are wary of its devilish properties, to the extent that many will under-treat even patients with terminal cancer. Like heroin, opium and modern narcotics, such as OxyContin, morphine blunts pain by weakening communication among spinal cord neurons, thus diminishing the transmission of pain signals.

Unfortunately, the power of morphine and other narcotics to block pain quickly fades with repeated use, a property called tolerance. Stronger and more frequent doses are necessary to achieve the same effect. Patients with chronic pain can become addicts, compounding their misery with debilitating drug dependency. Doc-

[DRUG TOLERANCE]

Glia Oppose Opiates

A stunning discovery made in recent years is that glia play a role in causing opiate painkillers to lose effectiveness. Linda R. Watkins of the University of Colorado at Boulder has demonstrated that morphine, methadone and probably other opiates directly activate spinal cord glia, causing glial responses that counteract the drugs' painkilling effects. The activated helper cells begin behaving much as they do after nerve injury, spewing inflammatory cytokines and other factors that act to overly sensitize neurons. Watkins showed that the effect starts less than five minutes after the first drug dose.

By making neurons hyperexcitable, glial influence overcomes the normal neuron-dampening effects of the drugs, explaining why patients often require ever increasing doses to achieve pain relief. The same mechanism may also underlie the frequent failure of opiates to relieve chronic neuropathic pain when it is driven by reactive glia. —R.D.F.



tors, fearing that they will be suspected of *dealing* rather than *prescribing* such large quantities of narcotics, are often forced to limit patients to dosages that are no longer effective in relieving their agony. Some patients resort to crime to obtain illegal prescriptions to ease their intolerable pain; a few turn to suicide to end their suffering. A new finding at the intersection of pain relief, glia and drug addiction is evidence that glia are responsible for creating tolerance to heroin and morphine.

Suspicious about glial involvement in narcotic tolerance first arose with the observation that just as when an addict quits heroin “cold turkey,” patients dependent on narcotic painkillers who stop their medication suddenly suffer classic painful withdrawal symptoms. The patients (and heroin addicts) become hypersensitive to such an extreme that even normal sound and light become excruciatingly painful. The similarity of these symptoms to the hyperesthesia seen in neuropathic pain suggested the possibility of a common cause.

In 2001 Ping Song and Zhi-Qi Zhao of the Shanghai Institute of Physiology tested whether the development of tolerance to morphine involved glia. When the researchers gave rats repeated doses of morphine, they saw the number of reactive astrocytes in the spinal cord increase. The changes in glia caused by repeated morphine injection were identical to those seen in the spinal cord after an injury or when neuropathic pain develops. The scientists then eliminated astrocytes with the same poison that Meller used to dampen the development of chronic pain in rats. Morphine tolerance in these animals was sharply reduced, indicating that glia in some way contribute to it.

Many research groups have since tried blocking various signals between neurons and glia (for example, by inactivating specific cytokine receptors on glia) and testing whether morphine tolerance is affected. This research shows that blocking inflammatory signals to and from glia does nothing to alter normal acute pain sensations, but if the blockers are injected together with morphine, lower doses of morphine are required to achieve the same relief *and* the duration of pain relief is doubled. These findings strongly indicated that glia were counteracting the pain-relieving effect of morphine.

Glia’s actions to undermine the potency of morphine are in keeping with the fundamental glial job of maintaining balanced activity in neural circuits. As narcotics blunt the sensitiv-

[DRUGS]

QUIETING OVERACTIVE GLIA

Several substances have been shown to modulate the activity of glia and are being tested as potential treatments for neuropathic pain or for the reduction of opiate tolerance and withdrawal. (Asterisks denote drugs already marketed for other uses.)

SUBSTANCE	MECHANISM	TESTING STAGE
AV411*	Inhibits astrocyte activity	Human tests for efficacy in enhancing morphine action and reducing withdrawal symptoms; safety tests for pain completed
Etanercept*	Anti-inflammatory signals quiet glia	Human tests for postsurgical neuropathic pain reduction
Interleukins* (cytokines)	Anti-inflammatory signals quiet glia	Cell and animal tests for pain
JWH-015	Activates pain-dampening CB2 cannabinoid receptors	Cell and animal tests for pain
Methionine sulfoximine*	Inhibits astrocyte neurotransmitter processing	Cell and animal tests for pain
Minocycline*	Inhibits activation of microglia	Cell and animal tests for pain
Propentofylline	Inhibits astrocyte activity	Human safety tests for pain completed
Sativex*	Activates cannabinoid receptors	Human efficacy tests for cancer-related and HIV-related neuropathic pain and diabetic neuropathy
SLC022	Inhibits astrocyte activity	Human efficacy tests for herpes-related neuropathic pain

➔ MORE TO EXPLORE

Could Chronic Pain and Spread of Pain Sensation Be Induced and Maintained by Glial Activation?

Elisabeth Hansson in *Acta Physiologica*, Vol. 187, No. 1–2, pages 321–327; published online May 22, 2006.

Do Glial Cells Control Pain?

Marc R. Suter et al. in *Neuron Glia Biology*, Vol. 3, No. 3, pages 255–268; August 2007.

Proinflammatory Cytokines Oppose Opioid-Induced Acute and Chronic Analgesia.

Mark R. Hutchinson et al. in *Brain, Behavior, and Immunity*, Vol. 22, No. 8, pages 1178–1189; published online July 2, 2008.

Pathological and Protective Roles of Glia in Chronic Pain.

Erin D. Milligan and Linda R. Watkins in *Nature Reviews Neuroscience*, Vol. 10, pages 23–36; January 2009.

ity of pain circuits, glia respond by releasing neuroactive substances that increase neuronal excitability to restore the normal levels of activity in neural circuits. Over time glial influence ratchets up the sensitivity of pain neurons, and when the blunting effect on pain circuits provided by heroin or narcotic pain medications is suddenly removed by rapid withdrawal from the drug, neurons fire intensely, causing supersensitivity and painful withdrawal symptoms. In experimental animals painful withdrawal from morphine addiction can be reduced dramatically by drugs blocking glial responses.

Modulating the activity of glia, then, could prove to be a key not only to alleviating chronic pain but also to reducing the likelihood that people treated with narcotic painkillers will become addicted. What a boon glia-targeted drugs would be for those who have long sought to control two such major sources of human misery and tragedy. Yet the connections among neurons, pain and addiction eluded scientists in the past who ignored the vital partner of neurons—glia. ■