

Why Migraines Strike

Biologists finally are unraveling the medical mysteries of migraine, from aura to pain

By David W. Dodick and J. Jay Gargus

KEY CONCEPTS

- Migraine is more than a headache: it is intensely painful and has distinct phases.
- The disorder used to be considered a vascular one, but recent research reveals it to be neurological, related to a wave of nerve cell activity that sweeps across the brain.
- The root of migraine may reside in brain stem malfunctioning.
- Although debate swirls about the precise cause of migraine, discoveries are already permitting the development of new treatments. —*The Editors*

For the more than 300 million people who suffer migraines, the excruciating, pulsating pain that characterizes these debilitating headaches needs no description. For those who do not, the closest analogous experience might be severe altitude sickness: nausea, acute sensitivity to light, and searing, bed-confining headache. “That no one dies of migraine seems, to someone deep into an attack, an ambiguous blessing,” wrote Joan Didion in the 1979 essay “In Bed” from her collection *The White Album*.

Historical records suggest the condition has been with us for at least 7,000 years, yet it continues to be one of the most misunderstood, poorly recognized and inadequately treated medical disorders. Indeed, many people seek no medical care for their agonies, most likely believing that doctors can do little to help or will be downright skeptical and hostile toward them. Didion wrote “In Bed” almost three decades ago, but some physicians remain as dismissive today as they were then: “For I had no brain tumor, no eyestrain, no high blood pressure, nothing wrong with me at all: I simply had migraine headaches, and migraine headaches were, as everyone who did not have them knew, imaginary.”

Migraine is finally starting to get the attention it deserves. Some of that attention is the result of epidemiological studies revealing just how common these headaches are and how incapacitating: a World Health Organization report described migraine as one of the four most disabling chronic medical disorders. Additional concern results from recognition that such headaches and their aftermaths cost the U.S. economy \$17 billion a year in lost work, disability payments and health care expenses. But most of the growing interest comes from

new discoveries in genetics, brain imaging and molecular biology. Though of very different natures, those findings seem to converge and reinforce one another, making researchers hopeful that they can get to the bottom of migraine’s causes and develop improved therapies to prevent them or halt them in their tracks.

The Ascent of Vapors

Any plausible explanation of migraine needs to account for a wide and varied set of symptoms. The frequency, duration, experience and catalysts of episodes differ greatly. Victims have, on average, one or two daylong attacks every month. But 10 percent get them weekly, 20 percent experience them for two to three days, and up to 14 percent have them more than 15 days a month. Often the pain strikes just one side of the head, but not always. Migraines in people prone to them can be set in motion by such a variety of events that they seem inescapable; alcohol, dehydration, physical exertion, menstruation, emotional stress, weather changes, seasonal changes, allergies, sleep deprivation, hunger, altitude and fluorescent lights are all cited as triggers. Migraines occur in all ages and both genders, yet women between the ages of 15 and 55 are disproportionately hit—two thirds of cases occur in this population.

Physicians over the years have proposed many reasons for why these headaches arise. Galen in ancient Greece attributed them to the ascent of vapors, or humors, from the liver to the head. Galen’s description of hemicrania—a painful disorder affecting approximately one half of the head—is indeed what we refer to as migraine today: the old word “hemicrania” eventually became “megrim” and ultimately “migraine.”



FOUR PHASES OF MIGRAINE

Unlike most headaches, migraine has distinct stages, although not all sufferers experience each one—a perplexing facet of the disorder.

60%	<p>PRODROME TYPICAL FEATURES: Difficulty concentrating, yawning, fatigue, and sensitivity to light and noise. DURATION: A few hours to a few days</p>
30%	<p>AURA TYPICAL FEATURES: Visual illusions of sparks and lights, often followed by blind or dark spots in the same configuration as the earlier bright hallucinations. DURATION: 20 to 60 minutes</p>
100%	<p>HEADACHE TYPICAL FEATURES: Excruciating pain accompanied by sensitivity to light and sound, nausea and vomiting. Sometimes the pain affects half the head. DURATION: 4 to 72 hours</p>
70%	<p>POSTDROME TYPICAL FEATURES: Persistence of sensitivity to light and movement, as well as lethargy, fatigue and difficulty focusing; some patients describe this as a “zombie” phase. DURATION: A few hours to a few days</p>

Percentage who report undergoing each phase

Blood flow replaced humors as the culprit in the 17th century, and this vascular hypothesis held sway, with few exceptions, until the 1980s. The accepted idea, based on the observations and inferences of several physicians, including Harold G. Wolff of New York–Presbyterian Hospital, was that migraine pain stems from the dilation and stretching of brain blood vessels, leading to the activation of pain-signaling neurons. Wolff thought the headache was preceded by a drop in blood flow brought about by the constriction of these same blood vessels.

Fresh observations from brain scans have altered understanding of the vascular changes. It turns out that in many the pain is preceded not by a decrease in blood flow but by an *increase*—an increase of about 300 percent. During the headache itself, though, blood flow is not increased; in fact, circulation appears normal or even reduced. Not only has the specific understanding of blood flow changed, but so has the prevailing view of the root of migraine. Migraine is now thought to arise from a disorder of the nervous system—and likely from the most ancient part of that system, the brain stem.

Aura's Origin

This newer insight has come mainly from studying two aspects of migraine: the aura, which precedes the pain in 30 percent of sufferers, and the headache itself. The term “aura” has been used for nearly 2,000 years to describe the sensory

hallucinations immediately preceding some epileptic seizures; for 100 years or so, it has also been used to describe the onset of many migraines. (Epilepsy may occur in people with migraine, and vice versa; the reasons are under investigation.) The most common form of aura is a visual illusion of brilliant stars, sparks, flashes of light, lightning bolts or geometric patterns, which are often followed by dark spots in the same shape as the original bright image. For some people, the aura can include a feeling of tingling or weakness, or both, on one side of the body as well as speech impairment. Usually the aura precedes the headache, but it may start after the pain begins and persist through it.

Aura appears to stem from cortical spreading depression—a kind of “brainstorm” anticipated as the cause of migraine in the writings of 19th-century physician Edward Lieving. Although biologist Aristides Leão first reported the phenomenon in animals in 1944, it was experimentally linked to migraine only recently. In more technical terms, cortical spreading depression is a wave of intense nerve cell activity that spreads through an unusually large swath of the cortex (the furrowed, outer layer of the brain), especially the areas that control vision. This hyperexcitable phase is followed by a wave of widespread, and relatively prolonged, neuronal inhibition. During this inhibitory phase, the neurons are in a state of “suspended animation,” during which they cannot be excited.

Neuronal activity is controlled by a carefully synchronized flow of sodium, potassium and calcium ions across the nerve cell membrane through channels and pumps. The pumps keep resting cells high in potassium and low in sodium and calcium. A neuron “fires,” releasing neurotransmitters, when the inward flow of sodium and calcium through opened channels depolarizes the membrane—that is, when the inside of the cell becomes positively charged relative to the outside. Normally, cells then briefly hyperpolarize: they become strongly negative on the inside relative to the outside by allowing potassium ions to rush out. Hyperpolarization closes the sodium and calcium channels and returns the neurons to their resting state soon after firing. But neurons can remain excessively hyperpolarized, or inhibited, for a long time following intense stimulations.

The phases of hyperexcitability followed by inhibition that characterize cortical spreading depression can explain the changes in blood flow that have been documented to occur before

VARIABILITY

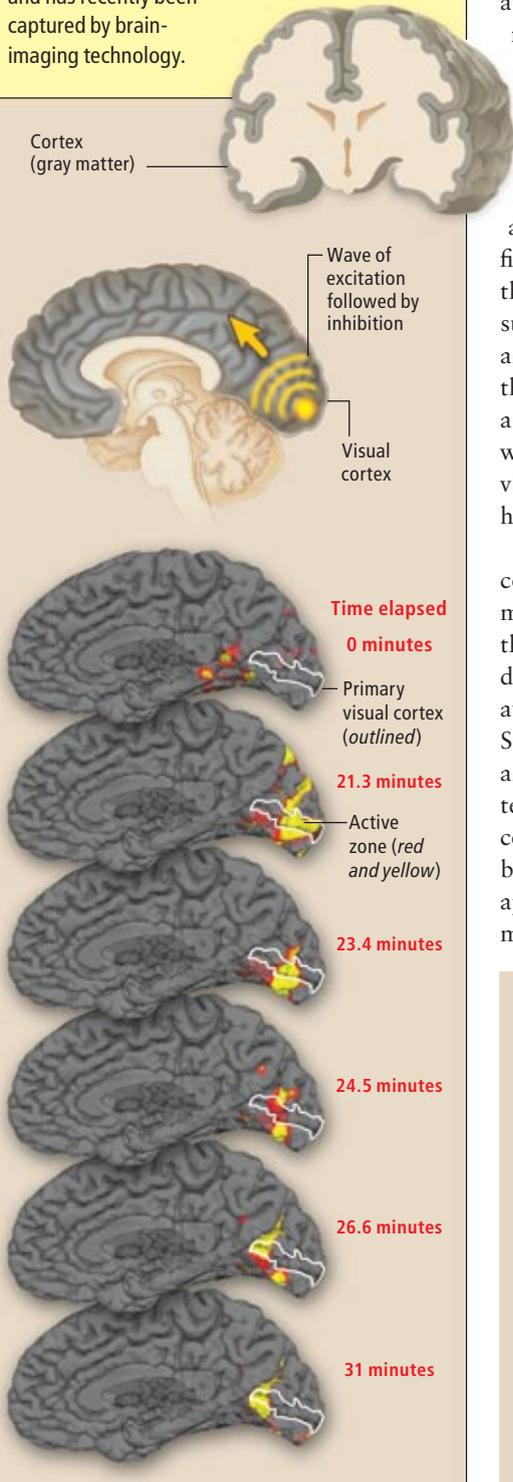
Victims experience attacks for different durations and at different frequencies. Most have migraines one or two days every month. But 10 percent have them weekly, and up to 14 percent get them more than 15 days every month. Two thirds of the world's 300 million migraine sufferers are women aged 15 to 55—suggesting estrogen plays a role.



[WHAT CAUSES AURAS]

A BRAINSTORM

Auras have been found to stem from cortical spreading depression: a wave of excessive signaling across large areas of the brain, followed by abnormal silence in the previously overactive areas. The spreading moves across the cortex at the rate of two to three millimeters a minute and has recently been captured by brain-imaging technology.



migraine pain sets in. When neurons are active and firing, they require a great deal of energy and, thus, blood—just what investigators see during brain scans of patients experiencing aura. But afterward, during inhibition, the quiet neurons need less blood.

Various other observations support the idea that cortical spreading depression underlies aura. When recorded by advanced imaging technology, the timing of the depolarizing wave dovetails neatly with descriptions of aura. The electrical wave travels across the cortex at a rate of two to three millimeters a minute, and the visual illusions that accompany aura are exactly those that would arise from an activation spreading across the cortical fields at just that rate. The suite of sensations that aura can entail—visual, sensory, motor—suggest that corresponding areas of the cortex are affected in sequence as the “storm” crosses them. The dark spots that patients experience after the bright hallucinations are consistent with neuronal inhibition in the regions of the visual cortex that have just experienced the hyperexcitability.

Genetic studies have offered a clue to why cortical spreading depression occurs in some migraine sufferers. Nearly all migraine is thought to be a common complex polygenetic disorder—in the same camp as diabetes, cancer, autism, hypertension and many other disorders. Such diseases run in families. Identical twins are much more likely to share migraine than fraternal twins are, indicating a strong genetic component. But the disease is clearly not caused by a single genetic mutation; rather a person apparently becomes susceptible by inheriting mutations in a number of genes, each probably

[THE AUTHORS]



David W. Dodick (left) and **J. Jay Gargus** (right) share a deep interest in understanding and ameliorating migraine. Dodick, a professor of neurology at the Mayo Clinic in Arizona, received his medical degree at Dalhousie University in Halifax, Nova Scotia. He studies the central nervous system abnormalities behind migraine and other forms of headache. Gargus, a professor of physiology, biophysics and human genetics at the University of California, Irvine, received his medical degree and doctorate at Yale University. He is studying the genetic underpinnings of migraine and other ion channel disorders.

AURAS take different forms, and many patients have sought to represent the hallucinations in their art. This depiction of an aura highlights the brightness and jaggedness that many people experience.



COURTESY OF DAVID W. DODICK (Dodick); UNIVERSITY OF CALIFORNIA, IRVINE, MEDICAL CENTER (Gargus); TAMII TOLPA (brain illustrations); COURTESY OF NOUCHINE HADJIKHANI (brain scans); MIGRAINE ACTION ASSOCIATION AND BOEHRINGER INGELHEIM (aura art)

[HYPOTHESES]

THE ROOT OF MIGRAINE PAIN

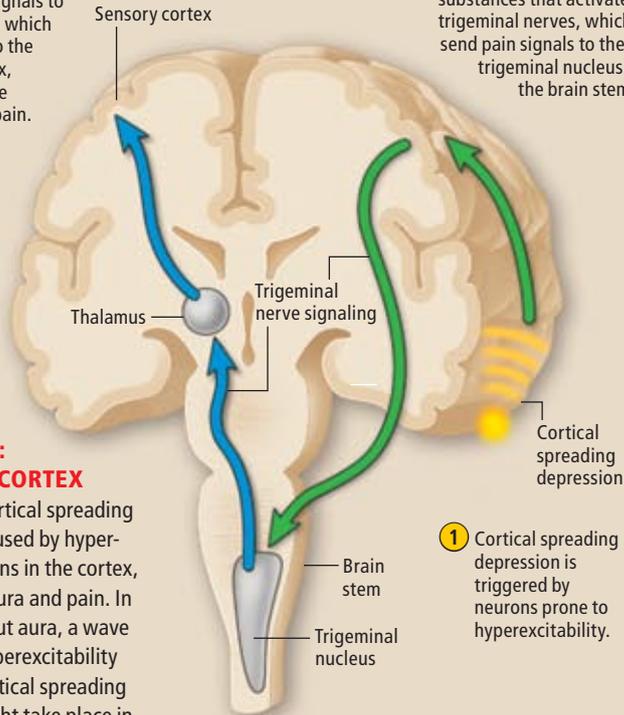
Whether headache is initiated by the brain stem, by the cortex or by the subcortex remains an active debate.

3 The trigeminal nucleus conveys the signals to the thalamus, which relays them to the sensory cortex, involved in the sensation of pain.

2 Those neurons release substances that activate trigeminal nerves, which send pain signals to the trigeminal nucleus in the brain stem.

SCENARIO 1: BLAME THE CORTEX

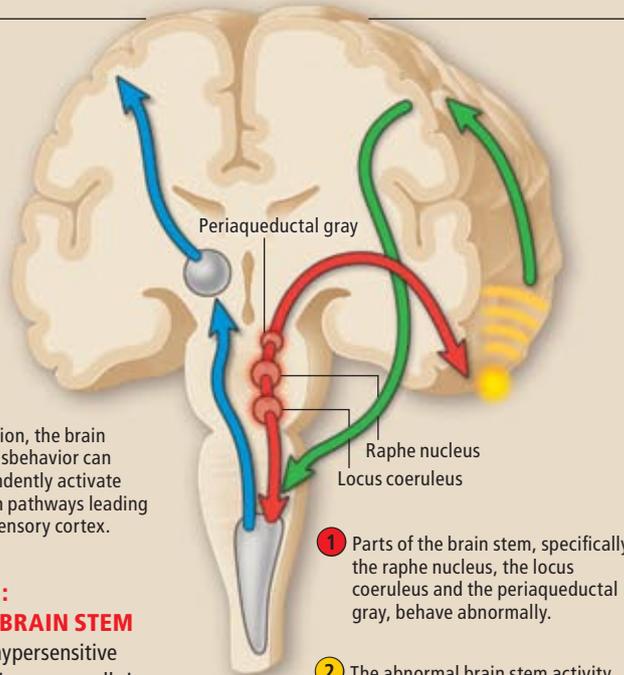
In this view, cortical spreading depression, caused by hypersensitive neurons in the cortex, induces both aura and pain. In patients without aura, a wave of neuronal hyperexcitability resembling cortical spreading depression might take place in subcortical regions.



1 Cortical spreading depression is triggered by neurons prone to hyperexcitability.

SCENARIO 2: BLAME THE BRAIN STEM

Alternatively, hypersensitive or malfunctioning nerve cells in three nuclei in the brain stem might be the catalyst.



1 Parts of the brain stem, specifically the raphe nucleus, the locus coeruleus and the periaqueductal gray, behave abnormally.

2 The abnormal brain stem activity triggers spreading depression in the cortex or subcortex, thereby activating the trigeminal system.

making a small contribution. Nongenetic components operate as well, because even identical twins are “discordant” for the disorder: sometimes one twin will suffer from migraine, and the other will not.

Investigators do not know which genes increase susceptibility to migraine and its aura in the general population, but studies of people affected by a rare form of the disorder, called familial hemiplegic migraine, indicate that flaws in neuronal ion channels and pumps cause the aura and pain in these patients. Notably, three genes have been shown to carry mutations that individually are potent enough to cause the disease—and all three encode neuronal ion channels and pumps. What is more, the genes are altered by mutations that increase the excitability of nerve cells, presumably by altering the properties of the encoded ion channels and pumps. These findings strongly support the idea that migraine could be a channelopathy, a newly recognized type of disease that arises from disturbances in ion transport systems—a known cause of ailments such as cardiac arrhythmia and seizures.

It is not clear whether malfunctioning ion pumps and channels are the only means by which aura can be produced. Nor is it clear that the common forms of migraine involve perturbations in the three genes implicated in familial hemiplegic migraine. But the genetic insights remain very exciting because they suggest a relation between cortical spreading depression and ion channel problems, one that could prove crucial to designing new medications.

From Aura to Ache

At the same time that researchers have been making headway in understanding the relation between aura and cortical spreading depression, they have been probing the source of migraine pain—the headache that is felt in those who experience aura as well as those who do not. The immediate source of the pain itself is obvious. Although most regions of the brain do not register or transmit pain signals, a network of nerves called the trigeminal nerve system does. These neurons carry pain signals from the membranes that surround the brain, called the meninges, as well as from the blood vessels that infuse the membranes. Pain is relayed through the trigeminal network to an area called the trigeminal nucleus in the brain stem and, from there, can be conveyed up through the thalamus to the sensory cortex, which is involved in our

awareness of pain and other senses. What first activates the trigeminal nerves in migraine, however, is under debate. There are essentially two schools of thought.

Some researchers contend that cortical spreading depression directly stimulates the trigeminal nerves. As the wave of hyperexcitability travels across the cortex, it brings about the release of neurotransmitters, such as glutamate and nitric oxide, as well as of ions. These chemicals serve as messengers that induce the trigeminal nerves to transmit pain signals. Researchers have observed in animals that cortical spreading depression does indeed activate the trigeminal nerves in this way.

That pathway to pain could even explain what happens in patients who do not experience aura. According to this view, cortical spreading depression might occur in areas of the cortex whose activation produces no outward symptoms before the onset of pain. Or spreading depression might occur in subcortical regions in certain people and stimulate the trigeminal nerves. In this case, although patients may not experience aura, the basic physiology would be the same as in those who do. Good evidence supports this hypothesis. Spreading depression can be evoked in laboratory animals in subcortical regions.

Moreover, the changes in cerebral blood flow that reflect the phases of cortical excitation and subsequent inhibition in migraine sufferers with aura have also been seen in people who experience migraine without aura; those patients, too, show a large increase in blood flow followed by normal or reduced flow. This finding raises the possibility that cortical spreading depression is fundamental to migraine but that only in some instances does it give rise to visual symptoms recognized as aura. Instead the process might generate less obvious symptoms, such as fatigue or difficulty concentrating. The finding may also explain why many people who experience aura will at times undergo attacks without it.

Other investigators place the root of migraine pain not in cortical or subcortical spreading depression but in the brain stem—Grand Central Station for information passing to and from the body and the brain. It is also home to the control center for alertness, perception of light and noise, cerebral blood flow, respiration, sleep-wake cycles, cardiovascular function and, as described earlier, pain sensitivity. Positron-emission tomography has revealed that three clusters of cells, or nuclei, in the brain stem—the



MIGRAINE has been around forever, as far as experts can tell. The 12th-century illuminated manuscript *Scivias* at the left portrays a vision described by theologian and abbess Hildegard of Bingen. It is thought to be one of the earliest representations of an aura.

locus coeruleus, raphe nucleus and periaqueductal gray—are active during and after migraine. According to this hypothesis, abnormal activity in those nuclei could induce pain in two ways. The nuclei normally inhibit trigeminal neurons within the trigeminal nucleus, continuously saying, in effect, “don’t fire.” The nuclei’s misbehavior could impair this ability and thus allow the trigeminal neurons to fire even when the meninges send no pain signals. In that situation, the trigeminal nucleus would relay pain messages to the sensory cortex in the absence of incoming pain signals from the meninges or blood vessels. The three nuclei might also trigger spreading depression.

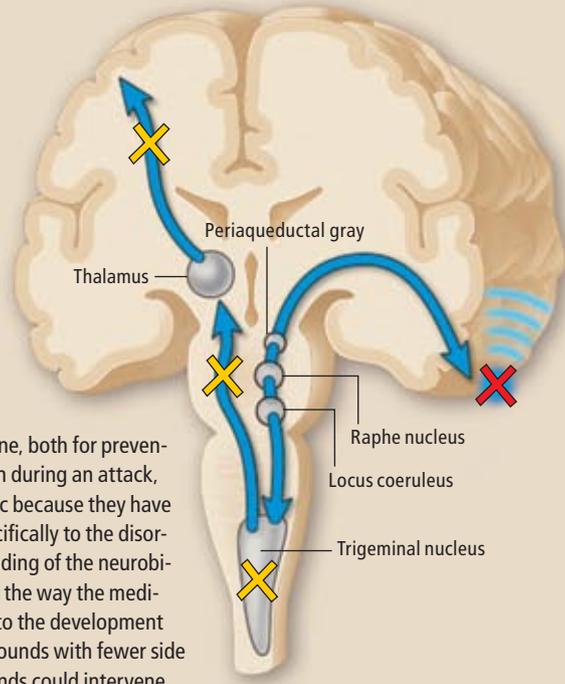
Researchers have noted that if one were to alter a part of the brain stem so as to bring about other symptoms of migraine as well, including aura, the place to do it would be these three nuclei. One of their most important functions is to control the flow of sensory information—such as light, noise, smell and pain—that reaches the sensory cortex. Occasional dysfunction in these clusters of cells could therefore explain why migraine sufferers may experience sensitivity to light, sound and odors.

In addition, the activity of these cells is modulated by the behavioral and emotional state of the individual—factors that can trigger migraines. These brain stem areas receive input from only two areas of the cortex, the limbic and paralimbic cortices, regions that regulate arousal, attention and mood. Through its con-

CATALYSTS

For unknown reasons, migraine can be set off by various triggers, including alcohol, perfume, dehydration, exercise, menstruation, stress, weather changes, seasonal changes, allergies, lack of sleep, altitude, flickering lights and hunger.

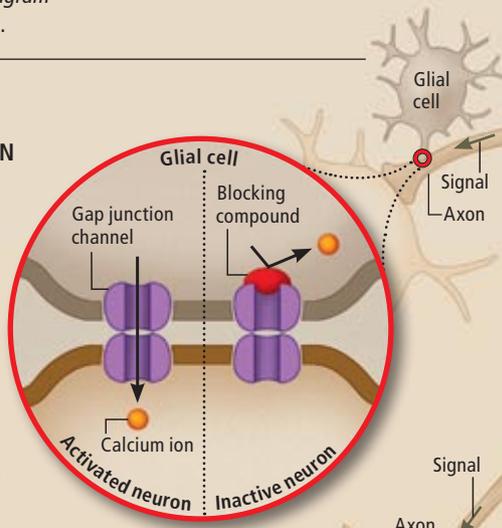
INSIGHTS REFINE THERAPIES



Treatments for migraine, both for prevention and for alleviation during an attack, have been problematic because they have not been tailored specifically to the disorder. Recent understanding of the neurobiology of migraine and the way the medicines work is leading to the development of more refined compounds with fewer side effects. Such compounds could intervene at various sites (marked on the diagram with Xs) and work in several ways.

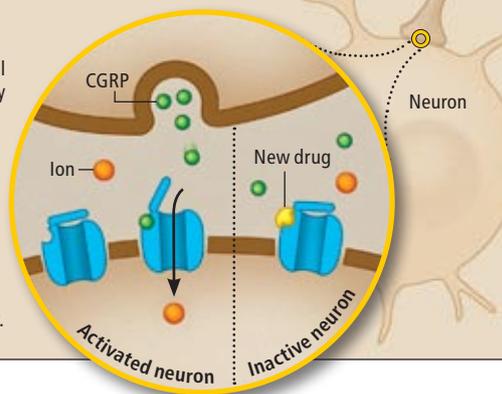
X INHIBIT CORTICAL SPREADING DEPRESSION

The wave of hyperexcitability called cortical spreading depression involves ion transfer from glia (a class of brain cell) to neurons, through a form of ion channel called a gap junction. Gap junctions allow calcium to flow between glia and neurons, which activates the neurons. Compounds currently in clinical trials close these cellular pores to stop the wave in its tracks.



X INHIBIT TRIGEMINAL NEURONS

One of the ways that trigeminal nerves convey pain signals is by releasing the neurotransmitter calcitonin gene-related peptide (CGRP), which activates neurons in the trigeminal nucleus. A class of drugs called triptans alleviates migraine by blocking the release of CGRP. New treatments in advanced trials block the effects of CGRP.



nection with the brain stem, the limbic cortex affects the functioning of the rest of the cortex—a fact that might explain how emotional and psychological stress could catalyze migraines, why mood fluctuates during migraine, and why there is an association between migraine and depression and anxiety disorders, both of which occur more commonly in migraine sufferers than in others.

Finally, the spontaneous, pacemakerlike activity of the raphe nucleus neurons—crucial to regulating pain pathways, circadian rhythms and sleep-wake cycles—depends on the perfect working of ion channels in neurons of that region and on the neurons' release of the neurotransmitters norepinephrine and serotonin into other brain areas. Such neurotransmission may be an ancient mechanism that is perturbed in migraine: experiments in the roundworm *Caenorhabditis elegans* have revealed that two genes very like those mutated in familial hemiplegic migraine are critical regulators of serotonin release. This finding opens the possibility that mutations in ion channels may lead to aberrant function in these brain stem areas and perhaps, as a result, to hyperexcitability in the cortical areas they influence.

The question then becomes, Does pain typically arise from the intrinsic hyperexcitability of cortical neurons (which leads to cortical spreading depression, activation of meningeal trigeminal pain fibers and the pain of a migraine)? Or does some glitch in brain stem activity incite the pain (by directly rendering the trigeminal neurons spontaneously active or by facilitating cortical spreading depression, or both)? The latter scenario is more convincing to some researchers because the pivotal control exerted by the brain stem over so many aspects of our experience could explain the varied symptoms of migraine.

What the Future May Hold

At the moment, only a few drugs can prevent migraine. All of them were developed for other diseases, including hypertension, depression and epilepsy. Because they are not specific to migraine, it will come as no surprise that they work in only 50 percent of patients—and, in them, only 50 percent of the time—and induce a range of side effects, some potentially serious.

Recent research on the mechanism of these antihypertensive, antiepileptic and antidepressant drugs has demonstrated that one of their effects is to inhibit cortical spreading depression.

The drugs' ability to prevent migraine with and without aura therefore supports the school of thought that cortical spreading depression contributes to both kinds of attacks. Using this observation as a starting point, investigators have come up with novel drugs that specifically inhibit cortical spreading depression. Those drugs are now being tested in migraine sufferers with and without aura. They work by preventing gap junctions, a form of ion channel, from opening, thereby halting the flow of calcium between brain cells.

The medicines prescribed for use during an attack have been as problematic as the ones used preventively. Triptans—as the class of drug is called—constrict blood vessels throughout the body, including coronary arteries, seriously limiting their use. These treatments were developed based on the mistaken idea that blood vessel dilation caused the pain and thus constriction was necessary to alleviate it.

It now appears that triptans ease migraine by interrupting the release of messenger molecules—specifically calcitonin gene-related peptide—from trigeminal nerves that feed signals into the trigeminal nucleus. The interruption blocks those trigeminal nerves from communicating with the brain stem's pain-transmitting network of neurons. It is also possible that triptans prevent such communication by operating

Clues from Genetic Studies

In recent years researchers have identified several gene mutations that underlie familial hemiplegic migraine, a rare, inherited form of migraine. Although the genetic work is in early stages, it is already clear that these mutations disrupt the complex workings of the ion channels and pumps that regulate the activity of nerve cells. The genetic findings have helped convince many investigators that even common forms of migraine arise from abnormal activity by nerve cells rather than from blood-flow changes in the brain. This conclusion is reinforced by the discovery that three "migraine genes" also carry mutations that cause epilepsy, one of the first heritable diseases recognized to result from abnormal ion channel functioning. Such diseases are called channelopathies. The genes implicated in the familial disorder include those listed below:

- *CACNA1A* encodes a major protein of a neuronal calcium channel called the P/Q channel.
- *ATP1A2* carries the information for producing a protein that pumps sodium and potassium ions across the membranes of nerve cells to create the ion gradient used by ion channels.
- *SCN1A* is the most recently discovered familial hemiplegic migraine gene. It gives rise to a neuronal sodium channel.

in the thalamus and the periaqueductal gray.

The new understanding of triptan activity has opened up possibilities for drug development, including a focus on calcitonin gene-related peptide. Several medicines that block the action of that pain-producing neurotransmitter are in clinical trials, and they appear not to constrict arteries. In addition, researchers are devising therapies that target other trigeminal neurotransmitters, such as glutamate and nitric oxide, in a further effort to interrupt the communication between trigeminal nerves innervating the meninges and the trigeminal nucleus in the brain stem. These compounds will be the first specifically designed to combat migraine during an attack by targeting neurons without constricting blood vessels.

Researchers have also examined nonpharmaceutical approaches. A handheld device that transmits brief pulses of magnetic stimulation is being evaluated, for example, for the treatment of migraine with and without aura. The premise is that this technology, called transcranial magnetic stimulation, or TMS, may interrupt cortical spreading depression and possibly prevent pain from arising or progressing.

For millions of people, these developments mark a breakthrough—not only in terms of relief from pain if all goes well but also in regard to attitudes about migraine. Scientists and physicians are finally coming to see migraine for the complex, biologically fascinating process it is and to recognize its powerfully debilitating effects. The disorder is "imaginary" no longer. ■

➔ MORE TO EXPLORE

Migraine. Oliver Sacks. Vintage, 1999.

Migraine—New Molecular Mechanisms. Daniela Pietrobon in *Neuroscientist*, Vol. 11, No. 4, pages 373–386; 2005.

Receptor, Transporter, and Ion Channel Diseases. J. Jay Gargus in *Encyclopedia of Molecular Cell Biology and Molecular Medicine*. Edited by Robert A. Myers. Wiley, 2005.

Chronic Daily Headache. David W. Dodick in *New England Journal of Medicine*, Vol. 354, No. 2, pages 158–165; January 12, 2006.

Recent Advances in Understanding Migraine Mechanisms, Molecules and Therapeutics. Peter J. Goadsby in *Trends in Molecular Medicine*, Vol. 13, No. 1, pages 39–44; January 2007.

ALICE IN WONDERLAND
author Charles Lutwidge Dodgson (known by his pen name, Lewis Carroll) suffered from migraines. Some contend that Alice's physical transformations are based on Dodgson's migraine experiences, because feelings of size distortion—technically called micropsia and macropsia—are described by many migraine patients.

