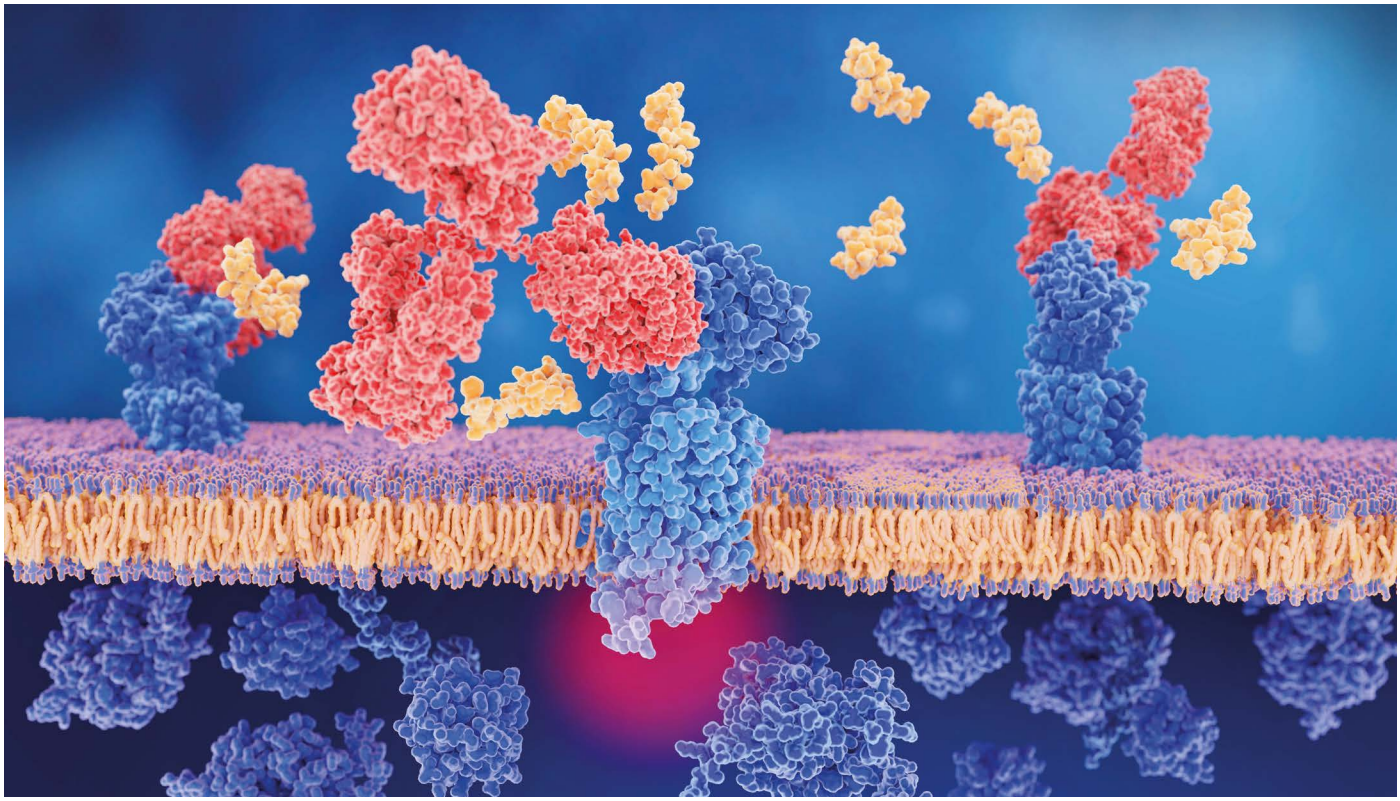

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Monoclonal antibodies (red shapes) against the calcitonin gene-related peptide receptor (blue) have revolutionized migraine treatment.

Refining a marvel

A new class of migraine drug is transforming some people's lives. But the treatments have the potential to do so much more. **By Marcus Woo**

Peter Goadsby sat in the audience, intrigued. The Australian medical student had come to Lund, Sweden, for a conference in June 1985. He was studying migraine, and during this particular talk about the trigeminovascular system – the network of nerves linked to blood vessels in the head – something clicked. This pathway, he realized, could be a way to understand migraine.

He introduced himself to the speaker, a physician at the local university hospital named Lars Edvinsson. Over coffee, the two discussed potential biomarkers for migraine in the trigeminovascular system – including a molecule called calcitonin gene-related peptide (CGRP) that had been discovered a few years previously. CGRP is a neuropeptide, which neurons use to communicate, and Edvinsson suspected it had a key role in migraine. The conversation launched a partnership that laid the clinical foundation for a class of drug that, 35 years later, is bringing relief to people with migraine.

"It started as a pursuit of a marker, of asking the question of what might be involved in the pain," says Goadsby, now a neurologist at King's College London. "It ended up being bigger than that."

Since 2018, the US Food and Drug Administration (FDA) has approved six drugs that block either CGRP or its receptor. The drugs are similarly effective to current therapies, but they have had a dramatic impact, thanks to their relative lack of side effects and the fact that they work for many people for whom other drugs fail. "They don't work for everybody by any means," says Andrew Charles, a neurologist at the University of California, Los Angeles. "But the potential for that kind of life-changing response is really something I've never experienced before."

Researchers are now looking to treat other kinds of headache with the same CGRP-targeted drugs. But despite the success of these drugs, the role of CGRP in migraine is not fully understood. By probing how the molecule contributes to the hypersensitivity to sensory inputs that is characteristic of migraine, researchers are teasing apart the complex underpinnings of the disease – which could lead to yet more therapies for migraine.

Common yet complex

Migraine is a common neurological disorder, affecting about 14% of the world's population. It is also highly debilitating. Migraine attacks can last for hours or even days, causing intense pain as well as sensitivity to light, sound, smell and touch. People must often contend with nausea and vomiting, and about one-quarter also experience visual disturbances known as aura (see page S7). Altogether, migraine is second only to lower-back pain in terms of years lost to disability, with medical expenses and lost productivity estimated to cost around US$80 billion in the United States each year. "I don't think it's appreciated widely enough

how troublesome migraine is," Goadsby says.

Unfortunately, because migraine is so complex, it has proved to be a difficult condition to treat. Many migraine therapies are drugs intended for other diseases. Antidepressants, anticonvulsants, blood pressure-lowering drugs and onabotulinumtoxin A — otherwise known as Botox — are all used to prevent migraine. In the 1990s, a class of migraine-specific drug called triptans emerged. These treat attacks as they happen by activating serotonin receptors, and provide at least two hours of pain relief for up to half of people with migraine.

CGRP-targeted drugs are similarly effective. In those who take them to prevent migraine, they almost entirely cease attacks for about 25% of people, says Edvinsson. Another 50% or so report moderate improvement, with fewer attacks, and the rest don't respond at all. "In general, these drugs are not more effective than the drugs we have already," says Jes Olesen, a neurologist at the University of Copenhagen. "But there are huge advantages with the new drugs."

The earlier drugs carry a risk of side effects, and even migraine-specific triptans can cause nausea, increased heart rate and fatigue. But the CGRP-targeted drugs used to treat acute-attacks so far seem to cause only minor side effects such as constipation, in just a small fraction of people.

There are some concerns, however, that because CGRP is also a potent dilator of blood vessels, blocking it might raise the long-term risk of stroke or heart attack. "The biggest question is whether people who have been on CGRP drugs for a long time get cardiovascular side effects," says Susan Brain, a pharmacologist at King's College London. Hints of adverse cardiovascular effects have been seen in mice, in which treatment with CGRP-receptor antagonists has been seen to worsen stroke[1], but studies in people have not yet found a problem. As Brain points out, that might be because most people with migraine are younger than 50 and therefore begin treatment with a relatively low risk of cardiovascular disease.

Another advantage of CGRP-targeted drugs is that they exploit a different mechanism from previous therapies. "We need many different drugs because one size doesn't fit all," Olesen says. For people who have tried every other migraine drug to no avail, CGRP-blocking drugs could provide desperately needed relief.

Journey of discovery

Soon after CGRP's discovery in 1982, Edvinsson and other researchers found that it was present in half of the nerves in the trigeminal ganglion — a structure of cell bodies that sits behind the face and serves as the sensory hub of the face and head.

At the time, migraine was considered to be a vascular disease, linked to the regulation of blood flow in the brain. Because CGRP was known to dilate blood vessels, Edvinsson reasoned that the molecule might be connected to migraine. Although research now indicates that migraine is instead neurological in origin, CGRP would still turn out to play a key part in migraine headache.

After their meeting in Lund, Goadsby worked with Edvinsson to move from studying animal models and tissue samples to patients. The pair took blood samples from the jugular vein of people experiencing a migraine attack, and again when the pain subsided. They found that levels of CGRP were elevated during an attack, before dropping back to normal when the attack was over[2]. They published their results in 1990, before strengthening the connection three years later in a study showing that sumatriptan, one of the new triptan migraine drugs at the time, reduces levels of CGRP[3].

"That kind of life-changing response is really something I've never experienced."

The link was further cemented in 2002, when a team of researchers triggered an attack in people susceptible to migraine by injecting CGRP[4]. "When the substance can do that," says Olesen, who was part of the study, "then you know you're pretty much in business."

Two years later, Olesen led a proof-of-concept study showing that a small molecule that blocks the receptor for CGRP could mitigate the symptoms of a migraine attack[5]. Other similar, more effective molecules, known as gepants, were later identified. Two of these received FDA approval in December 2019 and February 2020 for the treatment of acute migraine, in the form of pills taken orally at the onset of an attack. The FDA has also approved four anti-CGRP monoclonal antibodies for the prevention of migraine: three in 2018 and one in February 2020. These must be injected monthly or quarterly.

Unpicking the mechanism

All of these drugs are designed to stop CGRP getting to its receptor, either by blocking the receptor or binding to CGRP itself. But exactly how that affects migraine is uncertain.

It is still unknown whether the drugs are blocking CGRP in the central nervous system (CNS; the brain and spinal cord) or in the peripheral nervous system: no evidence conclusively points either way. It seems unlikely that the fundamental mechanism for a disorder as complex as migraine resides in just the peripheral nerves, Goadsby says.

Rodent experiments suggest that CGRP does act in the brain. But the CNS is protected by the blood–brain barrier (BBB), which prevents large particles — such as CGRP antibodies — from entering. Gepants are considerably smaller: if the antibodies were the size of an American football, gepants would be as small as a grain of rice, Edvinsson says. Even so, only a small proportion of them pass through the BBB.

Most migraine researchers therefore suspect that these drugs interfere with CGRP outside the CNS, such as in the trigeminal nerves or the meninges — the layers between the brain and skull — where migraine pain might originate.

Perhaps the simplest theory is that CGRP sensitizes these peripheral nerves, which in turn send signals to the CNS that induce the pain and sensitivity to sensory stimuli associated with migraine. The question for researchers now is "how exactly it is doing that", says Andrew Russo, a neuroscientist at the University of Iowa in Iowa City.

One possibility is that when CGRP binds to its receptor, it sensitizes the nerves by increasing their rate of firing. In addition, as Russo and others propose, CGRP could trigger an inflammatory response. For example, CGRP could cause glial cells (non-neuronal cells in the nervous system) and nearby immune cells to release inflammatory compounds, such as cytokines. These compounds could alter the environment around the nerve endings and make them more sensitive to sensory input. CGRP might also induce the release of such compounds from vascular cells in blood vessels.

Furthermore, CGRP might activate pain receptors by dilating blood vessels. When the vessels dilate in the trigeminal ganglion, Russo says, they could push on pain receptors on adjacent nerves. These receptors respond to pressure and release pain signals, which in turn trigger the release of more CGRP in a feedback loop.

Even the gastrointestinal tract might be involved in how CGRP acts in migraine. In some people, certain foods can provoke a migraine attack. The CGRP antibody erenumab can cause constipation, and a study co-authored by Olesen showed that injecting CGRP led to gastrointestinal issues such as diarrhoea. "It's possible that CGRP is acting in the gastrointestinal tract, and that is a trigger

COURTESY OF LARS EDVINSSON

Lars Edvinsson (left) and Peter Goadsby (centre) at a neurology meeting in the early 1990s.

for attacks in some people," says Greg Dussor, a neuroscientist at the University of Texas at Dallas.

Beyond migraine

Despite the lingering uncertainty over exactly how CGRP-targeted drugs alleviate migraine, researchers and clinicians are exploring whether they can be made to work more broadly. For example, whereas CGRP antibodies prevent migraine attacks and gepants treat acute attacks, at least one drug might do both. In March, Biohaven Pharmaceuticals in New Haven, Connecticut, revealed promising results of a phase III trial for migraine prevention with rimegepant, a gepant that was already approved to treat acute migraine. Unlike the antibodies, which must be injected, rimegepant comes in a pill, and would be easier to take. "This is starting to blur the distinction between acute treatment and preventative treatment," Charles says.

Researchers are also exploring the use of CGRP-targeted drugs in children with migraine. Clinical trials of the antibody erenumab in children are now recruiting. Ahead of that, Charles has already treated some children with the drugs. "Our practical experience in children is that they can be highly effective," he says. "But we haven't systematically proven that."

The drugs are also finding use in alleviating other disabling headache disorders such as cluster headaches, in which intense pain can strike several times per day for weeks or even months at a time (see page S15). In 2018, a study showed that injecting people who experience cluster headache with CGRP induced an attack[6]. The next year, following a clinical trial, the FDA approved the use of the CGRP antibody galcanezumab to treat episodic cluster headaches.

CGRP could also prove to be a useful target in the treatment of headaches that arise after a head injury. "There's a very good chance it will be helpful for post-traumatic headache," Charles says. Many symptoms of concussion, such as dizziness and light sensitivity, are similar to those that accompany a migraine, and researchers have shown that CGRP antibodies can prevent these symptoms from appearing in concussed rodents. In June, researchers published the first clinical trial demonstrating that the CGRP antibody erenumab could help to lower the frequency of post-traumatic headaches in people[7].

There is less optimism, however, for tension headaches. These are fundamentally different from migraine, Goadsby says. People with tension headaches tend to have only pain and no hypersensitivities, and concentrating on a task can provide relief – the opposite effect to that seen in migraine. Some researchers are marginally more hopeful. Russo, for instance, notes that some migraine attacks start with a tension headache, suggesting that there might be some biological overlap. And Dussor points out that tension headaches might be associated with tightening muscles in the neck and head, which can affect the surrounding sensory nerve fibres and release CGRP. But it is unclear how significant a role CGRP might have, if any. "For tension headache, I don't think it's going to work," Russo said. "But it will be fascinating to find out."

Vast possibilities

CGRP is not the only molecule implicated in migraine. "It just happened to be the one that was identified early," Dussor says. The very fact that drugs that target CGRP do not work for every person with migraine – and do not usually completely eliminate migraine even in those who do respond – suggests that other molecules are involved. "This is too complex of a disorder to be one of a single peptide," he says.

Another neuropeptide that is already captivating researchers is pituitary adenylate cyclase-activating peptide (PACAP). Like CGRP, it is a vasodilator found in the trigeminal nerve. And also like CGRP, levels of PACAP rise during migraine attacks. In addition, PACAP injections can induce migraine-like attacks in people who have experienced migraines before, and mild to moderate headaches in others. As a result, several drug companies are developing and testing PACAP antibodies in clinical trials.

PACAP could be just the start. There are already 100 known neuropeptides, and more than 1,000 peptides overall are encoded in the human genome. Most of them probably have no connection to migraine, but the vast numbers suggest open possibilities. "I think there's going to be many other peptides involved in migraine," says Russo, who has identified a dozen candidates. Multiple peptides could mean multiple peptide-blocking drugs – and relief for those who don't respond to anti-CGRP drugs.

The story of CGRP has been one of success. Before it, without anything concrete to quantify or define the disorder, migraine had been met with a dismissive attitude, according to migraine researchers. "The discovery that CGRP was involved in migraine is so important because it was the first step to establish the biochemistry behind migraine," Russo says.

The journey has been especially gratifying for Edvinsson and Goadsby, who have spent their careers leading the translation of basic research into a drug they now use to treat patients. "I never thought I'd live to see the day where I'd write a prescription for something for which I've been involved with the idea," Goadsby says. Patients write letters and send flowers expressing gratitude, Edvinsson says. "It's like their lives had been grey, and suddenly they see the sun."

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