Antibodies Linked to Rare Epilepsy

A rare but serious form of childhood epilepsy turns out to be caused by an immune attack on the brain, a discovery that suggests new approaches for its treatment

It starts with a small seizure, perhaps no more than the twitch of a child's eye or mouth. But over months or at most a few years, the seizures spread and grow in frequency and strength. Eventually they may come 100 times a day or more and take over half the brain, leaving the child weak, demented, unable even to speak.

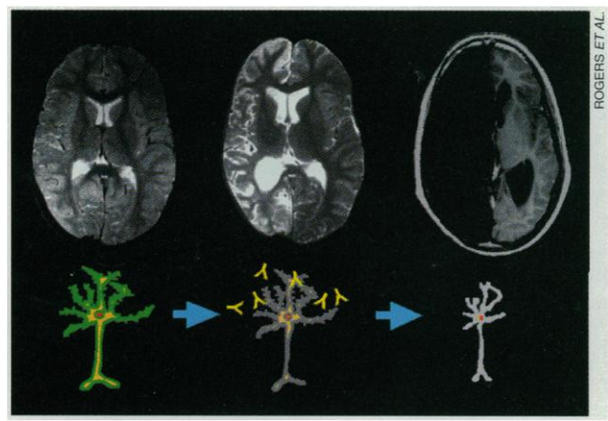
This is the clinical picture presented by Rasmussen's encephalitis, a devastating—although mercifully rare—form of childhood epilepsy. The only reliable treatment is shockingly severe: hemispherectomy, removal of the entire affected half of the child's brain. But recent research seems to have identified a cause for this previously poorly understood disease, and with that discovery have come new strategies for treatment.

Last year, a team led by neurobiologist Scott Rogers of the University of Utah in Salt Lake City found that children with Rasmussen's encephalitis have antibodies to the receptor through which glutamate, an excitatory neurotransmitter found throughout the brain, stimulates nerve cells. This suggested that the condition might be an autoimmune disease, caused by an attack on the brain by the body's own antibodies (*Science*, 29 July 1994, p. 648).

Now the Rogers team has drawn even tighter the chain of evidence for an autoimmune cause for Rasmussen's. In the April issue of *Neuron*, they report that the antibodies found in Rasmussen's patients don't just recognize and bind glutamate receptors—they act as glutamate itself does, turning the receptors on. This is the first known case of autoantibodies activating a neurotransmitter receptor, and it raises the possibility that the antibodies may directly trigger seizures in Rasmussen's patients, by overstimulating glutamate receptors.

That discovery may be the tip of the iceberg, because new findings show that Rasmussen's encephalitis isn't the only neurological disease in which patients form antibodies to the glutamate receptor. In the March issue of *Molecular Medicine*, Rogers and his colleagues report that patients with a rare autoimmune neurological disease known as paraneoplastic neurodegenerative syndrome (PNS) also make antibodies that bind to, and alter the activity of, glutamate receptors.

The new results are "fascinating," says Washington University neuroscientist Dennis Choi, who studies the role of glutamate receptors in neurological disease. "They raise a whole set of [possibilities of] linking what are fundamentally immune disorders to neurodegenerative processes and to other kinds of changes in central nervous system function." They also suggest that it may be possible to treat Rasmussen's, and possibly PNS as well, either by preventing the antibodies from getting to the brain or by finding ways to block their effects on the glutamate receptor.



ROGERS *ET AL.*

Overactive. Antibodies stimulating brain neurons may cause the hyperactivity *(light areas)* seen in early *(left)* and late *(middle)* Rasmussen's encephalitis. The only treatment now is hemispherectomy *(right)*.

All these developments trace their origins to a sick rabbit. In 1991, Rogers, then a postdoc in the Salk Institute laboratory of Stephen Heinemann, and Lorise Gahring, a postdoc at the Scripps Research Institute, were immunizing rabbits with pieces of glutamate receptors to raise antibodies they could use to study the receptors. In July, Rogers heard from the animal room that one of the rabbits was sick. "When I got there, it was almost dead," says Rogers. "There was blood all over."

The blood was from the rabbit's tongue, which had been badly bitten. James McNamara, a neurologist and epilepsy specialist from Duke University who was visiting Heinemann's lab on sabbatical, said the rabbit appeared to have had a seizure. A second rabbit that had been immunized with the same receptor fragment also seemed ill, although not as severely so. Rogers began surveillance of the second rabbit with a video camera and found that it was having frequent minor seizures.

Rogers sent the rabbits' brains to Duke, where McNamara and neuropathologist Barbara Crain examined them and found they had been infiltrated by immune cells. "I said there is only one disease I know of that is characterized by epileptic seizures and this histopathology," says McNamara, "and that is Rasmussen's encephalitis."

The onset of the disease in the recently immunized rabbits made it seem that the antibodies were the cause. That, says Rogers, triggered a sense that history was repeating itself: Two decades earlier, Jon Lindstrom and Jim Patrick, also at Salk, found that rabbits immunized with the acetylcholine receptor developed muscle weakness and paralysis reminiscent of the human disease myasthenia gravis. That finding led to the discovery that myasthenia gravis is caused by autoantibodies attacking the acetylcholine receptors on muscles. "We went to school on their finding," says Rogers.

Following that earlier example, McNamara and neurologist Ian Andrews sent serum from four Rasmussen's patients to Rogers and Gahring, who had moved to the University of Colorado Medical Center in Denver in late 1991, and to another team member, Tom Hughes, at the University of California, San Diego. Both groups tested the serum for antibodies to GluR3, the glutamate receptor subunit used to immunize the ill-fated rabbits. Three of the four children had the antibodies; the one who didn't was in remission.

That suggested that antibodies to GluR3 might be causing, or at least exacerbating, the epilepsy, and spurred McNamara and Andrews to try plasma exchange, a therapy for autoimmune diseases that filters antibodies from the blood, on a nine-year-old girl with Rasmussen's who was having 10 or so major seizures a day. "She just lay in bed waiting for the next seizure," says McNamara. "She didn't read or write or talk or play or go to school or anything."

The girl's response to the plasma exchange was so dramatic that McNamara compares it to the film, *Awakenings*. After several treatments, "she walked, she talked, she read, she wrote," he says. "The improvement was absolutely extraordinary." Rogers

and Gahring monitored the girl's anti-GluR3 antibodies and found that they dropped as her condition improved. But, as often occurs with plasma exchange, the treatment lost effectiveness over several months, and the girl relapsed. The team reported the results in last July's *Science* paper.

Meanwhile, Rogers and Gahring had moved to the University of Utah in 1993. There they teamed up with neurologist Roy Twyman, who applied the antibodies to cultured neurons and found that the antibodies activate glutamate receptors. This was the first case of autoantibodies activating a receptor for a neurotransmitter.

That finding, reported in the *Neuron* paper, suggests a model for how Rasmussen's might develop. Normally, the blood-brain barrier, which surrounds blood vessels in the brain, prevents antibodies from reaching brain tissue. But Rasmussen's often begins with a mishap such as a bump on the head or a fever, which can cause a leak in the barrier. That wouldn't be a problem ordinarily, but if a child had autoantibodies to the glutamate receptor, the antibodies could enter the brain and activate the receptors, exciting neurons and causing a seizure. A vicious cycle could then develop, because seizures themselves cause rifts in the blood-brain barrier, allowing more antibodies and inflammatory immune cells into the brain and intensifying the immune attack.

Given that Rasmussen's starts locally and "eats its way out, like Pac-Man," says pediatric neurologist John Freeman of Johns Hopkins University, the idea that the disease starts from a small breach of the blood-brain barrier seems "very logical." It is less clear, says Freeman, whether GluR3 antibodies start the process, or "whether there is something else which causes focal autoimmune disease, and as you damage neurons, you have GluR3 released, and you form antibodies to it." But Lindstrom, now at the University of Pennsylvania, points out that "you can model the disease by immunizing an animal [with GluR3]. That is very good evidence," he says, that the GluR3 antibodies are causal.

Rasmussen's is a very rare disease, affecting only a handful of children each year. But McNamara speculates that "a small subset" of cases of more common forms of epilepsy may be autoimmune as well. University of Pennsylvania neurologist Marc Dichter agrees. The Utah and Duke teams are both working to develop a simple test for glutamate receptor antibodies that would allow wide screening of patients. "Once the antibody test becomes more available, I would guess we would see more patients with uncontrolled focal epilepsy who will fit into this category," Dichter says.

Glutamate receptor antibodies have also been found in another group of neurological patients, those with PNS, a very rare condition in which a tumor—often of the lung, ovary, or breast—causes the body to make autoantibodies to various parts of the brain. The Utah group teamed up with University of Utah neurologist John Greenlee, who studies the condition, and examined the serum of PNS patients. They reported in last month's issue of *Molecular Medicine* that six of seven patients had antibodies, not to GluR3, but to several other glutamate receptor subunits.

Moreover, Twyman found that, while the antibodies alone don't activate the glutamate receptors as GluR3 antibodies do, they make the receptors hypersensitive to glutamate. Because overactive glutamate receptors can kill neurons, the antibodies could contribute to the progression of PNS, says Greenlee. But he cautions that "we haven't proven that's what happens." If such a mechanism were proven, however, it might provide an important key to intervention.

Intervention based on the current findings seems to be closer at hand for Rasmussen's patients than for those with PNS. Indeed, since last July's *Science* paper, a handful of neurologists, including Dichter and McNamara, have had some success using plasma exchange and other treatments for autoimmune disease on Rasmussen's patients. They have just submitted their results for publication.

But complicating the clinical decision-making is the fact that there are no foolproof therapies for autoimmune diseases at present, and if a patient may need a hemispherectomy eventually, it is better done soon, because a younger brain is better at adapting. Removing the left hemisphere of the brain of a child more than 10 years old carries with it a serious risk that language skills will not transfer to the right side of the brain. And removal of either hemisphere becomes riskier the older the child gets.

Because of that risk, Freeman and his colleague Eileen Vining have just scheduled two Rasmussen's patients, both nine-year-olds, for hemispherectomy. Nevertheless, Freeman laments, "it does seem incredibly dumb to be taking out half the brain for an autoimmune disease." At least this rare syndrome is now hitched to the bandwagon of autoimmune diseases, where the search for better treatments is intense. And so the days of hemispherectomies may be numbered.

–Marcia Barinaga

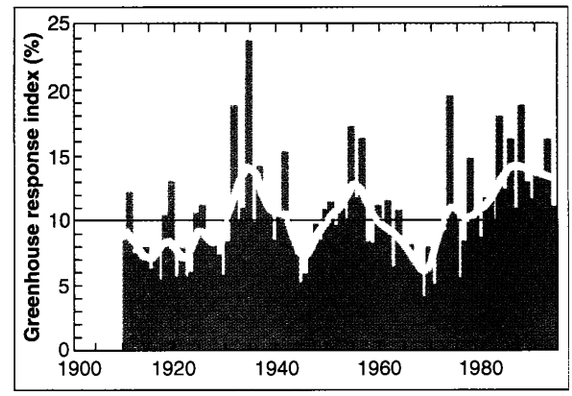
CLIMATE

U.S. Climate Tilts Toward the Greenhouse

Yellowstone was ablaze during the torrid, parched summer of 1988. The Midwest was awash in the great floods of '93. Minneapolis was shivering with a wind chill of –32°C this April. Is this wild and woolly weather a sign that a strengthening greenhouse effect is changing global climate? That possibility is on everyone's lips during a scorching summer or a season of floods, but no single weather event can be conclusive. Only when unsettled weather becomes a persistent trend can it say anything about global change. Now Thomas Karl, senior scientist at the National Climatic Data Center in Asheville, North Carolina, and his NCDC colleagues have found such a pattern—a sign, they say, that the U.S. climate has turned toward a greenhouse regime in the past 15 years.

By combining data on summer droughts, wet winters, drenching rainstorms, and other weather extremes expected to grow more common in a warmer climate, Karl and his colleagues have come up with the Greenhouse Climate Response Index, a handy one-number guide to the state of the U.S. climate. As they report in the premiere issue of *Consequences*, a journal of global change, the index has been stuck at a high level ever since the late 1970s, suggesting that chance variation may not be enough to explain the unusual weather of recent years.

"The trend directions we see in the U.S. are indeed what's projected" for an intensified greenhouse, says Karl. "You shouldn't judge the whole world from the U.S. standpoint, and even in the United States it's not so overwhelming that you'd say the evidence is unequivocal." Still, by showing that recent weather trends are just what you would expect from a greenhouse warming, the index should help give the public and policy-makers a better feel for what global climate



On the wild side. A U.S. climate index based in part on weather extremes has jumped toward values expected in a greenhouse warming. The expected value is 10%.