Back to (brain) basics

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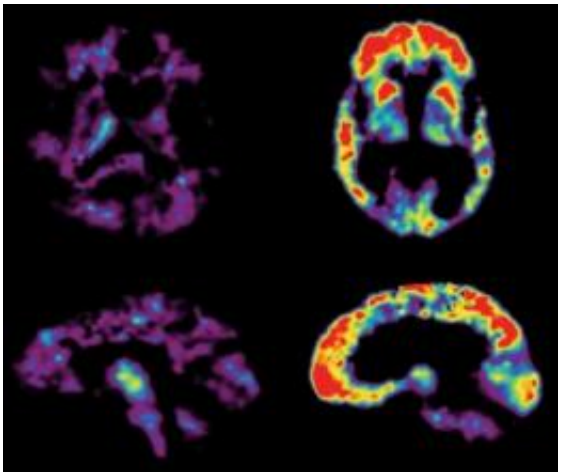

PET Scans Showing PiB Uptake in the brain of a cognitively healthy person (left) and in the brain of a person with AD (right). Images courtesy of the Alzheimer's Disease Education and Referral Center

(PhysOrg.com) -- In his own words, MIT neuroscientist Mark Bear admits he did not "wake up one day and say 'Hey, I'm going to cure autism.'" But, after decades of painstaking basic research on how the brain rewires itself in response to external cues, Bear has discovered a way to reverse the symptoms of Fragile X Syndrome, a disorder that can cause autism, mental retardation and epilepsy.

“It was a classic payoff of basic research,” says Bear, the Picower Professor of Neuroscience.

And Bear is not the only MIT neuroscientist discovering this payoff.

Several basic research projects have recently yielded drugs now in clinical trials to treat a variety of brain disorders. Helped by advances in lab technology, neuroscientists have learned enough about how the brain works that they can start coming up with ways to treat problems that arise when something goes wrong, says Mriganka Sur, head of MIT's Department of Brain and Cognitive Sciences.

"A lot of basic science is abstract, and necessarily so, but I foresee that as neuroscientists, we can have as much impact on brain disorders as biologists have had on cancer," says Sur, whose own research has led to potential treatments for Rett Syndrome, a specific type of autism.

Making connections

One of neuroscience's major goals is unraveling the mechanisms of human learning and memory — a daunting task. One way that brain scientists narrow their approach is to target the connections between individual neurons, known as synapses.

At these synapses, neurotransmitters such as glutamate, dopamine or serotonin carry messages from one brain cell to another. Those chemicals set off a variety of responses in the receiving cell, such as electrical signals or producing another signaling molecule.

Sometimes the messages enact changes to the synapses themselves, usually a strengthening or weakening of the connection — a phenomenon known as synaptic plasticity. This plasticity forms the basis of learning and memory.

In the late 1980s, Bear's research suggested that a cell receptor — called a metabotropic glutamate receptor — plays a critical role in synaptic plasticity. He was intrigued by its role in a phenomenon known as long-term depression, a suppression of synapses that helps shape brain

connections during development. However, he had no inkling that it would lead him to a potential way to reverse autism symptoms.

“I had no idea what Fragile X was. None,” he says.

Many years later, after the Human Genome Project was completed, researchers linked Fragile X Syndrome to a gene that codes for a protein produced when synaptic metabotropic glutamate receptors are activated. After several years of experimentation, Bear realized that Fragile X protein actually inhibits the response to metabotropic glutamate receptors. When the fragile X protein is missing, overactivity of these glutamate receptors leads to excessive synaptic connectivity, protein synthesis, growth and excitability — all symptoms of Fragile X.

To prove his theory, Bear and his students crossed mice with Fragile X symptoms with mice that were genetically engineered to have fewer metabotropic glutamate receptors. The offspring were normal, showing that knocking out the glutamate receptor could reverse the symptoms of Fragile X.

“It was unbelievable,” Bear recalls. “It is absurd to think you could correct a disorder as varied as Fragile X by this one mechanism.”

This kind of result shows the value of the National Institute of Health’s approach to funding basic research, Bear says. In effect, the NIH is saying “keep working under the hood and I’m sure you’re going to find something important someday,” says Bear.

Four drug companies, including one co-founded by Bear, are now testing drugs that inhibit glutamate receptors in Fragile X patients.

Successes like these prove the value of basic research, says Constantine Stratakis, director of scientific programs for the NIH’s National Institute

of Childhood Health and Human Development. In fact, the lines between basic and clinical research are becoming increasingly blurred, he says. “There is no question that everything we do in clinical science is based on basic science,” says Stratakis.

‘Holy Grail’

Research in Sur’s lab has followed a similar arc. Clinical trials will start later this year for drugs based on Sur’s research on Rett Syndrome, which began as an effort to understand plasticity in neurons that process vision.

That work led naturally to studying brain disorders such as autism, because “disorders of development are disorders of how the brain is wired,” says Sur. “That’s why autism is so fascinating to me, because it maps so directly onto plasticity.”

So far, this approach of linking specific molecules to disease treatment has been most successful for specific types of autism caused by mutation of a single gene, such as Rett Syndrome and Fragile X Syndrome. However, Sur and Bear hope their work could also extend to other forms of autism someday.

“You need the basic science background to pursue treatments for these disorders, which has always been the Holy Grail for most if not all health sciences research,” says Sur.

In the laboratory of Li-Huei Tsai, director of MIT’s Picower Institute for Learning and Memory, recent advances have led to promising potential treatments for Alzheimer’s disease. Using a unique mouse model developed in her lab, she has shown that inhibiting a specific enzyme involved in brain plasticity can dramatically improve cognitive performance. A company called In Vivo, in Waltham, Mass., is now

conducting phase I clinical trials of one such inhibitor.

Tsai is optimistic about those trials, and also believes there are many other brain disorders — such as post traumatic stress disorder, schizophrenia, and bipolar disorder — that could be treated with similar drugs. “Nothing can be more rewarding than knowing that what you do may one day benefit people who suffer from these devastating diseases,” she says.

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