Researchers uncover new details about how signals are transmitted in the brain

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An international team of scientists has announced a new breakthrough in understanding the molecular details of how signals move around in the human brain. The work is basic research, but could help pharmacologists design new drugs for treating a host of neurological disorders, as well as drugs for reducing alcohol and nicotine craving.

Reporting in the November 11 issue of the journal *Nature*, researchers from the California Institute of Technology and the University of Cambridge explain how they have learned to force a protein known as the 5-HT3 receptor to change its function by chemically changing the shape of one of the amino acids from which it is built. Using a technique developed at Caltech known as "unnatural amino mutagenesis," the researchers altered a proline amino acid in the 5-HT3 protein in order to modulate the receptor's ion channel. This gave the researchers control of the "switch" that is involved in neuron signaling.

According to Dennis Dougherty, lead author of the paper and the Hoag Professor of Chemistry at Caltech, the new research solves a 50-year-old mystery of how a neuroreceptor is changed by a chemical signal. Scientists have long known that signaling in the brain is a chemical process, in which a chemical substance known as a neurotransmitter is released into the synapse of a nerve and binds to a neuroreceptor, which is a protein that is found in the surface membranes of neurons. The action of the neurotransmitter changes the neuroreceptor in such a way that a signal is transmitted, but the precise nature of the structural change was unknown until now.

"The key is that we've identified the switch that has to get thrown when the neuroreceptor sends a signal," Dougherty says. "This switch is a proline."

The 5-HT3 receptor is one of a group of molecular structures in the brain cells that are known as Cys-loop receptors, which are associated with Parkinson's disease, schizophrenia, and learning and attention deficit disorders, as well as alcoholism and nicotine addiction. For treatments of some of these conditions, pharmacologists already custom-design drugs that have a general effect on the Cys-loop receptors. But the hope is that better design at the molecular level will lead to much better treatments that address more precisely the underlying signaling problems.

Dougherty says the work required the collaboration of organic chemists, molecular biologists, electrophysiologists and computer modelers. His Caltech group worked closely with the research group of Caltech biologist Henry Lester, and with the group at Cambridge headed by Sarah Lummis, to establish how proline changes its structure to open an ion channel and launch a neuron signal.

"This is the most precise model of receptor signaling yet developed, and it provides valuable insights into the nature of neuroreceptors and the drugs that modulate them," Dougherty says.

"The promise for pharmacology is that precise control of the signaling could lead to new ways of dealing with receptors that are malfunctioning," says Lester, Caltech's Bren Professor of Biology. "The fundamental understanding of how this all works is of value to people who want to manipulate the signaling."

The 5-HT3 receptor is also involved in the enjoyment people derive from drinking alcohol. If the 5-HT3 receptors are blocked, then

alcoholics no longer get as much pleasure from drinking. Therefore, better control of the signaling mechanism could lead to more potent drug interventions for alcoholics. The nicotine receptors are also related, so progress could also lead to better ways of reducing the craving for nicotine.

In addition to Dougherty, Lester, and Lummis, the other authors of the paper are Caltech graduate students Darren Beene (now graduated) and Lori Lee, and Cambridge researcher William Broadhurst.

Source: Caltech