MedicalXpress

Scientists create entirely new way to study brain function

July 15 2009

(PhysOrg.com) -- Scientists at Duke University and the University of North Carolina have devised a chemical technique that promises to allow neuroscientists to discover the function of any population of neurons in an animal brain, and provide clues to treating and preventing brain disease.

With the technique they describe in the journal *Neuron* online on July 15, scientists will be able to noninvasively activate entire populations of individual types of neurons within a brain structure.

"We have discovered a method in which systemic administration of an otherwise inert chemical to a mutant mouse selectively activates a single group of neurons," said James McNamara, M.D., chairman of the Duke Department of Neurobiology and co-senior author of the paper. "Elaborating on this method promises to let scientists engineer different kinds of mutant mice in which single groups of neurons will be activated by this chemical, so scientists can understand the behaviors mediated by each of these groups."

Right now, most scientists gain knowledge of brain function by correlating brain activity with certain behaviors; connecting a damaged brain area with an observed loss of function; or activating entire brain structures invasively and observing the resulting behavior.

Knowing what a particular type of neuron in a specific brain region does will help researchers find the root of certain diseases so they can be

effectively treated, said McNamara, an expert in epilepsy. He pointed out that the human brain contains billions of neurons that are organized into thousands of distinct groups that need to be studied.

Four years ago, co-senior author Bryan Roth, M.D., Ph.D., and colleagues at UNC set out to create a cell receptor activated by an inert drug, but not by anything else. "Basically we wanted to create a chemical switch," said Roth, who is the Michael Hooker Distinguished Professor of Pharmacology at UNC-Chapel Hill.

"We wanted to put this switch into neurons so we could selectively turn them on to study the brain," said Roth, who was trained as a psychiatrist. "At the time, this idea was science fiction."

They used yeast genetics to evolve a specific receptor that could react with a specific chemical, because yeast quickly produces new generations. "If the theory of evolution were not true, this experiment would not have worked," Roth added.

The lab then worked to create a similar receptor in mice. In the initial attempt to create mice that expressed the receptor, the lab targeted receptor expression to neurons in the hippocampus and cortex of the brain. The receptor was designed to be activated by the drug clozapine-N-oxide (CNO), which has no other effects on the mice and no effects on normal neurons, those without the receptor.

Roth asked a student to inject the mice with CNO. They expected to register some type of change in neuronal activity, but were very surprised to see the mice have seizures. Suddenly, they had a model for studying epilepsy.

Roth immediately looked for epilepsy experts to collaborate with and contacted McNamara at Duke. Together they worked on this system that

allowed them to regulate the activity of neurons in mice with CNO that was injected and able to cross the blood-brain barrier to access deep-brain neurons. With this model, the scientists were able to examine neuronal activity leading to seizures and activity that occurred during seizures.

This receptor was designed for experimental use with animals. "Based on what we learn from animal models of disease, we could get better target treatments for humans," said Georgia Alexander, Ph.D., a postdoctoral fellow in Duke Neurobiology and co-lead author. "The great thing about these drug-activated receptors is that they can be applied to study any disease state, not just epilepsy. With this, you could try to selectively activate other populations of neurons, in an animal model of Parkinson's disease, for example." Roth said that the technique is not limited to neurons and brains, and is being used to study other cells in the body as well.

Alexander said researchers now can ask which areas of the brain are most susceptible to and critical to seizure generation, "because we can use similar techniques to inactivate or silence neurons, too."

For example, some people with seizures have a portion of their temporal lobes removed from their brains. "Now we can ask, 'Is there a different part of the brain or population of neurons we could selectively silence that would be an even better way to treat epilepsy patients?'" Alexander said.

Source: Duke University Medical Center (news : web)