MedicalXpress

Study opens the door to new class of drugs for epileptic seizures

July 29 2010

A chemical compound that boosts the action of a molecule normally produced in the brain may provide the starting point for a new line of therapies for the treatment of epileptic seizures, according to a new study by scientists at The Scripps Research Institute.

"This compound really provides a new angle for developing drugs to treat seizures," says Scripps Research Assistant Professor Xiaoying Lu, who co-authored the paper with Professor Edward Roberts, Chair of the Molecular and Integrative Neurosciences Department Tamas Bartfai, and colleagues.

As described this week in Proceedings of the National Academy of Sciences *(PNAS)*, the new compound effectively reduced the frequency and severity of seizures in mice and rats.

About 50 million people worldwide are affected by epilepsy, a disease characterized by recurrent, unprovoked seizures. As a result of the seizures, people may have violent muscle spasms or lose consciousness and, in some cases, suffer from brain damage or die. Epileptic seizures are caused by the rapid and excessive firing of a population of neurons in an area of the brain known as the cortex. The dozen-plus medicines currently on the market to treat epilepsy work to reduce this excessive firing primarily by targeting the mechanisms by which neurons send signals to one another.

However, as many as 30 percent of people with epilepsy do not respond

to current drugs, making the search for additional drugs that act by different mechanisms an urgent one.

Enter Galanin

A promising new approach to treating seizures is to target a molecule called galanin. Galanin is a peptide, a fragment of a protein, produced in the brain to regulate a variety of functions, such as pain, memory, addition, mood, and appetite. In the late 1990s, researchers discovered that galanin is also a potent anticonvulsant.

Recent research suggests that when seizures occur the brain steps up production of galanin, possibly as a way to protect itself against the seizures. As a result, mice engineered to lack galanin are more susceptible to developing seizures.

Because galanin seems to play a role in reducing seizures, several groups of researchers, including those at Scripps Research, have been working to develop drugs that target the galanin system.

The first category of such compounds consists of synthetic molecules that mimic galanin's functions (called agonists) and include Galnon, developed by Bartfai's group. Galnon and other galanin agonists have been shown to act as anticonvulsants when given to animals that were rendered prone to developing seizures. But these agonists have several drawbacks as potential therapeutic agents. For one thing, because Galnon acts relatively broadly, it may have unwanted side effects.

A New Mechanism

Lu, Roberts, Bartfai, and colleagues at Scripps Research have now designed a compound that targets the galanin system but, unlike the

previous agonists, is more selective in its action. The compound, dubbed CYM2503, binds to one of the three receptors for galanin on nerve cells, the galanin receptor type 2 (GalR2). On its own, CYM2503 has no effect on GalR2, but when galanin also binds to the receptor, CYM2503 boosts galanin's function.

The researchers tested the effects of CYM2503 on mice and rats that had received a chemical causing them to have seizures. The animals that received CYM2503 took longer to get the seizures and, when they did, the seizures lasted for a shorter time. Most importantly, when the researchers looked at the animals after 24 hours, the rats that had been treated with CYM2503 had a dramatically higher survival rate than those that had not.

This mechanism of action, modifying a receptor's function, is common to many successful drugs that have been developed for the treatment of a number of conditions, including epilepsy, hyperparathyroidism, and AIDS, but not yet for drug candidates targeting galanin system.

"It is a double breakthrough," says Bartfai. "The compound is a first new mode-of-action anticonvulsant and it represents a new mechanism of molecular action."

Because CYM2503 only works when galanin, a natural molecule, is also present, the researchers predict it will have fewer side effects than drugs that work on their own. This study provides the first evidence that modulating the GalR2 receptor is an effective strategy for treating seizures, thus opening the door for the development of drugs that target this mechanism.

"Based on the known functions of the GalR2 receptors, it may also work in treating depression and in protecting the brain from damage," says Lu.

Roberts adds, "This is an area we can now move into. We plan to go systematically through other conditions."

Provided by The Scripps Research Institute