MedicalXpress

Research uncovers promising target to treat chronic abdominal pain

March 2 2009

High levels of a protein linked to the way pain signals are sent to the brain led to a decrease in abdominal pain in a recent study in mice.

Researchers say the finding suggests the protein might someday serve as the basis of new treatments for chronic pain associated with a number of bowel disorders.

The scientists at Ohio State University found that nearly twice the normal amount of this protein, called EAAT2, or excitatory amino acid transporter 2, decreased what is called visceral pain, or pain from internal organs, in mice.

The protein acts on glutamate, an amino acid and neurotransmitter that sends signals to the brain that produce pain. The researchers found that a high level of EAAT2 appears to force glutamate into cells, preventing it from interacting with receptors that enable it to send the pain signals.

Though the researchers understand what EAAT2 does, there is still more to learn about the location of its activity and the complete mechanism behind the protein's role. But they are hopeful about the protein's potential to treat the pain caused by a variety of gastrointestinal disorders suffered by millions of Americans.

The most common condition is irritable bowel syndrome, a disorder characterized by cramping, abdominal pain, bloating, constipation and diarrhea. Experts estimate IBS affects between 10 percent and 20

percent of the U.S. population.

Visceral pain in bowel disorders is often difficult to treat because there is no clear structural problem or disease process to remedy, said Robert Stephens, associate professor of physiology and cell biology at Ohio State and senior author of the study.

"The question is, why does this unexplained pain exist? Pain usually signals something is wrong. But this functional pain is chronic pain without a reason. It is pain that makes people miss work and it's pain that is associated with depression. That's why we really want to get at it with these therapies," Stephens said.

The research is published in a recent issue of the *American Journal of Physiology - Gastrointestinal and Liver Physiology*.

Stephens and colleagues tested the effects of higher-than-normal levels of EAAT2 in two different types of mice. They used mice genetically engineered to produce an excess of the protein as well as normal mice that were treated with an antibiotic already known to generate extra EAAT2 in the body. The transgenic mice had about twice the normal level of EAAT2, and those treated with the drug produced between 40 percent and 80 percent more of the protein than would a normal mouse.

Both the transgenic mice and mice treated with the antibiotic that increases EAAT2 experienced less pain than did control mice that had normal levels of EAAT2 in their system. In both types of mice with elevated levels of EAAT2, the pain response was reduced by approximately 50 percent to 70 percent compared to the pain levels in normal mice.

To further prove that EAAT2 was responsible for the reduced pain response, the scientists pretreated mice with dihydrokainate (DHK), a

compound known to block the effects of that particular protein. The DHK significantly reversed the blunted pain response in mice with elevated levels of EAAT2.

Stephens said this approach appears to be effective for visceral pain only, and not for somatic pain, which is pain resulting from injuries to the skin, superficial tissues or muscles and bones.

The transgenic mice engineered to contain higher-than-normal levels of the protein are otherwise healthy. Stephens said that observation, combined with the fact EAAT2 does not affect somatic pain, suggest the protein is a good candidate for a therapy specifically designed to treat visceral pain.

"The drugs we have now aren't good. Really, all that's available is symptomatic treatment for irritable bowel syndrome. We just don't understand enough about what has gone wrong in these patients," he said.

The antibiotic ceftriaxone used in the study to increase EAAT2 levels may not be optimal IBS therapy because chronic antibiotic use could lead to bacterial resistance and overgrowth of other substances, such as yeast, Stephens said. However, this drug is now in Phase III clinical trials for the treatment of amyotrophic lateral sclerosis, also known as Lou Gehrig's disease.

Stephens is collaborating with other investigators who are studying compounds that have the same effect as the antibiotic in elevating EAAT2. Researchers also are exploring the use of inactive viruses to administer the protein as a therapy. With these methods, viruses are engineered to maintain their invasive abilities without causing an infection, and serve as a delivery system for a therapeutic agent.

The scientists next plan to find out where these key interactions between

EAAT2 and glutamate occur. Glutamate is present throughout the body, but Stephens and colleagues believe the spinal cord is the most likely site of action for blunting the pain response.

Source: Ohio State University