April 13, 2017

The Big Pore Theory could cure chronic pain

By Elodie Gazave

Cornell University researchers have produced for the first time an image of P2X7, a receptor associated with chronic pain. Visualizing the shape of the receptor has also allowed them to make a second groundbreaking discovery: They observed that five painkiller molecules they tested did not bind the receptor at the place they expected, which could explain why these painkillers lack efficacy in human patients.

This discovery, published Dec. 9, 2016, in the journal eLife, lays the foundations to create targeted and effective molecules to manage chronic pain.

Chronic pain affects 10 percent of the adult population. It also accompanies conditions such as rheumatoid arthritis and migraine, for which pain management remains crucial in patient care. However, chronic pain does not always respond to existing analgesic drugs.

The lack of effective medicines is partly due to the limited knowledge scientists have about pain. Cornell researchers have been looking into a receptor called P2X7, which binds a molecule called ATP.

Many drugs targeting P2X7 work by competing for space with the ATP molecule, occupying the groove at the surface of P2X7 where ATP would naturally bind. Scientist believe that preventing ATP from binding to the P2X7 receptor should block the pain signal.

Research in animal models had shown promising results for drugs targeting P2X7. However, clinical trials in humans were much less satisfactory.

To understand why these trials failed in humans, a team led by Toshimitsu Kawate, assistant professor in the College of Veterinary Medicine's Department of Molecular Medicine, decided to visualize the shape of the receptor. The results were astonishing, he said: "The drugs were not where we expected them to bind. We were actually shocked."

To make this discovery, Kawate and his team had to see the structure of the receptor. Using X-ray crystallography at the Cornell High Energy Synchrotron Source (CHESS), Kawate created an image of the receptor at a resolution of 3.5 angstroms – about a thousandth of the width of hair.

They found that P2X7 is an "elegant" molecule comprising three dolphin-shaped subunits. The "dolphin's fluke" of the three subunits is anchored in the cell membrane. These flukes work as a "camera shutter" that can twist open or close – a motion triggered by ATP.

In absence of ATP, the flukes form a closed conformation. When ATP molecules bind to the dolphin's upper body, the flukes rotate in a spiraling motion and form a pore in the cell membrane, allowing water, ions and other small molecules to pass through.

P2X7 has one interesting particularity compared with other ion-channel proteins. It mainly functions as a normal pore, but sometimes it converts into a big pore and allows molecules up to 900 dalton, a unit that quantifies mass at atomic levels, through the membrane.

STORY CONTACTS

Cornell Chronicle
George Lowery
607-255-2171
gpl5@cornell.edu

Media Contact
Melissa Osgood
607-255-9451
mmo59@cornell.edu

This big pore conversion process is what Kawate wants to study next to learn why and how frequently big pore conversion happens. Some theorize that under pathological conditions, big pore conformation might be what creates pain. For example, pain-causing molecules could be released from inside the cell to the surrounding tissues through the P2X7 channel. Kawate is trying to design genetic or chemical traps to capture P2X7 big pores so that he can visualize the structure and understand their biological significance.

Understanding under which physiological conditions and how the conversion happens may help manipulate the receptor, for example to design small molecules that can trap P2X7 and prevent its conversion to a big pore state. “This could be useful to treat several types of chronic pain, for example associated with irritable bowel syndrome, that are proposed to be caused by the big pore of P2X7.”

Elodie Gazave is a freelance science writer.