

Researchers 'see' structure of open nicotinic acetylcholine ion channels

April 7 2008

The neurotransmitter acetylcholine is an essential chemical communicator, carrying impulses from neurons to skeletal muscle cells and many parts of the nervous system. Now researchers at the University of Illinois have painstakingly mapped the interior of a key component of the relay system that allows acetylcholine to get its message across. Their findings, which appear in the current issue of *Nature Structure & Molecular Biology*, reveal how the muscle nicotinic acetylcholine receptor responds to a burst of acetylcholine on the surface of a cell.

The muscle nicotinic receptor is a neurotransmitter-gated ion channel. This “gate” regulates the flow of information, in the form of charged particles, or ions, across the cell membrane. Although normally closed, when the ion channel encounters acetylcholine – or nicotine – on the surface of the cell the interaction causes the gate to open, allowing positively charged ions (called cations) to flow into the cell.

Scientists have tried for decades to understand the mechanism that allows these channels to open. Using cryo-electron microscopy, in which samples frozen at extremely low temperatures are examined under an electron microscope, some researchers obtained images of the closed ion channel. Others used X-ray crystallography to image the closed-channel conformation. This technique involves crystallizing the protein, creating a lattice that reveals many details of its three-dimensional structure.

But until the Illinois team developed a new method for probing the interior of the open channel, no studies had been able to infer the

structure of the open channel conformation in a living cell. The Illinois team was able to do this by exploiting electrical properties of these membrane proteins.

Much like the flow of electrons through an electrical wire, the flow of ions through a cell membrane is a current. In the 1970s, two German researchers developed a technique for measuring the current through a single ion channel, an innovation that won them a Nobel Prize in 1991. Claudio Grosman, a professor of molecular and integrative physiology at Illinois, and Gisela D. Cymes, a postdoctoral associate in his lab, adopted this technique, and predicted that they could use it as a tool for what they call “in vivo, time-resolved structural biology.”

In a study published in 2005, the Grosman lab showed that ionizable amino acids (that is, those that may alternately be charged or neutral) can be engineered into the inner lining of the channel pore. These changes to the amino acid sequence alter the current, revealing the structure of the open-channel conformation in unprecedented detail.

“As the ionizable amino acids bind and release protons from the watery environment, the pore gains or loses a positive charge that interferes with the normal flow of cations through the channel,” Grosman said.

After analyzing the data, Grosman’s team demonstrated that the discrete changes in current reflect the position of each mutated amino acid in the channel and the extent to which water molecules penetrate the membrane protein.

This approach allowed Grosman’s team to map the relative position of every amino acid that formed the ion channel.

The new study extends this work to more distant portions of the protein.

After comparing these findings to direct studies of the structure of the closed channel, Grosman concluded that the conformational changes that allow the channel to open are quite subtle. The five subunits that make up the protein channel do not rotate or pivot dramatically when opening the gate.

“There are many good reasons why I think a subtle conformational change is advantageous from an evolutionary point of view,” Grosman said.

Muscle nicotinic receptors must respond to acetylcholine with staggering speed, opening within microseconds of their exposure to the neurotransmitter.

“These ion channels are meant to be quick,” he said. “If they are too slow, we have disease.”

Grosman said that the approach developed in his lab is the first to allow scientists to infer the structure of an ion channel in its open conformation as it functions in a living cell.

“I know when the protein is open, because in single-molecule experiments the distinction between open and closed conformations is simple; the channel either passes a current or not,” he said.

In a living cell the protein responds, in measurable ways, to changes in its structure and environment, he said. “It’s not frozen at super low temperatures. It’s not in a crystalline lattice. The cells are alive at the beginning of the experiment and when we finish the experiment, the cells keep living.”

Source: University of Illinois at Urbana-Champaign

Citation: Researchers 'see' structure of open nicotinic acetylcholine ion channels (2008, April 7)
retrieved 10 April 2024 from
<https://phys.org/news/2008-04-nicotinic-acetylcholine-ion-channels.html>

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