MedicalXpress

New study has implications for understanding ion channel defects

February 1 2010

(PhysOrg.com) -- A University of Wisconsin School of Medicine and Public Health team has made a discovery important to the millions of people who are on common medications for heart and neurological diseases.

The discovery relates to ion channels, key molecular players that generate and control electrical signals critical for heart, brain and other types of cells to do their jobs. If anything goes wrong in the process, called excitability, potentially deadly heartbeat abnormalities and epilepsies may arise.

As reported in the current (January 31, 2010) *Nature Structural & Molecular Biology*, the researchers have shown how the structure that couples the two main parts of sodium ion channels may allow them to communicate.

The study, which addresses a central question in ion channel biology, has important implications for understanding the many genetic mutations that cause ion channel defects resulting in debilitating and at times fatal diseases.

"Some 40 percent of all drugs used for treating heart and neurological diseases are ion channel modifiers or blockers," says lead author Baron Chanda, PhD, assistant professor of physiology.

The researchers focused on the voltage sensor of the sodium ion channel,

which first detects electrical voltage outside the cell, and the pore, which then responds to sensor signals by opening a small hole in the cell membrane.

Depending on the cell type, sodium, calcium, potassium or chloride ions will pass through the pore in milliseconds, entering the cell to promote muscle contraction, the exchange of neurotransmitters or other cell functions. When the pore shuts, the flow of ions - and that activity - stops.

"We wanted to know how electrical changes at the cell membrane translate into mechanical changes in the pore," Chanda says, noting that sodium ion channels are similar to, but more complicated than, other ion channels.

Chanda and his team zeroed in on the structure that connects the voltage sensor and the pore, a protein region called the gating interface, which consists of a series of amino acids.

They used a novel experimental method that allowed them to simultaneously observe the movement of the voltage sensor and the pore. Most previous studies were unable to see both activities at once.

The researchers mutated 55 amino acids in the gating interface to see which were most important for communication between the voltage sensor and the pore. They identified seven that clearly appear to play a role in the two-way conversation.

Most of the important amino acids were found in an unexpected location within the flexible regions of the gating interface, on elastic hinges with spring-like action that were attached to rigid segments extending into both the pore and voltage sensor.

"Our theory is that these hinges behave almost like a door closer," Chanda explains. "When the voltage sensor moves, it generates a strain in the gating interface that pulls the pore open."

When the researchers introduced bulky material, tryptophan, into the hinges, it blocked the swinging process that's necessary for the voltage sensor and the pore to couple and communicate.

The findings clarify how breakdowns in this process can occur if the key amino acids in the connecting gating interface are altered, as they presumably do in human mutations leading to disease.

Knowing how the mutations affect this process, and where they occur, should help future scientists develop better treatments for abnormalities in ion channel excitability that underlie many diseases.

Yukiko Muroi and Manoel Arcisio-Miranda of the physiology department were the co-first authors on this study and Sandipan Chowdhury from UW-Madison biophysics graduate training program also contributed.

Provided by University of Wisconsin-Madison