

Nicotine rush hinges on sugar in neurons

When nicotine binds to a neuron, how does the cell know to send the signal that announces a smoker's high?

As with other questions involving good sensations, the answer appears to be sugar.

A University of Southern California study appearing with a commentary in *Nature Neuroscience* online proposes a role for sugar as the hinge that opens a gate in the cell membrane and brings news of nicotine's arrival.

Structural biologist Raymond Stevens of The Scripps Research Institute, who was not involved in the study, called it "a landmark accomplishment for the fields of structural biology and neuronal cell signaling."

Besides substance addiction, Stevens pointed to epilepsy, schizophrenia and depression as targets for improved drugs that could result from the study's findings.

The study provides the first detailed look at part of the mouse nicotinic acetylcholine receptor (nAChR), one in a large and important group of molecules, known as ion channel proteins, that allow signals to pass between neurons.

The results reveal an important role for the sugar molecules in such proteins.

"Our studies fill a major gap in the field and set a new paradigm," said Lin Chen, associate professor of molecular and computational biology at USC.

Many existing theories, which do not consider sugar's role, are probably incomplete, Chen said.

The debate over how signals pass from the outside of a cell to the inside is a long-standing one.

Some researchers had suggested that when a chemical such as nicotine binds to an ion channel protein on the cell surface, the protein starts a "conformational wave" that propagates a signal through the protein body to the cell membrane, Chen said.

But the molecular basis of such a wave in nAChR or any other protein has not been clearly established.

Instead, the Chen group's study of crystal structure suggested a simple mechanical role for sugar molecules attached to the surface of the receptor.

"They serve as the link between the neurotransmitter binding site and the membrane region where the gate is located," Chen said.

"The sugar is kind of like a hinge. It's pulling the door open and closed."

Cutting the sugar chains stopped the gate's operation, according to Chen, who said, "The sugar is critical, in my opinion."

The researchers also found a water molecule deep in the receptor's core – significant because proteins normally are filled with hydrophobic (water repellent) matter that helps the structure hold its shape, Chen said.

The water molecule may enable the receptor to alter its shape in counterbalance to the bending hinge, said Chen, who explained, "Think of it as a lubricant."

Previously studied "homologs" of nAChR – proteins that share its structure but not its signaling function –

are entirely hydrophobic, Chen said, supporting the theory that the buried water molecule plays a functional role.

Chen called the group's *Nature Neuroscience* study "one of the few times that you felt that you connected the dots."

The study also represents a tour de force of protein crystallography. Homologs of nAChR had been studied at the atomic scale, but not the receptor itself.

Source: University of Southern California

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