Uncovering the 3-D structure of a key neuroreceptor

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EPFL scientists reveal for the first time the 3D structure of a crucial neuroreceptor. The achievement has great implications for understanding the basic mechanism of electrical signal transmission between neurons and might help to design novel medicines to treat various neurological diseases.

Neurons are the cells of our brain, spinal cord, and overall nervous system. They form complex networks to communicate with each other through electrical signals that are carried by chemicals. These chemicals bind to structures on the surface of neurons that are called neuroreceptors, opening or closing electrical pathways that allow transmission of the signal from neuron to neuron. One neuroreceptor, called 5HT3-R, is involved in conditions like chemotherapy-induced nausea, anxiety, and various neurological disorders such as schizophrenia. Despite its clinical importance, the exact way that $5HT_3$-R works has been elusive because its complexity has prevented scientists from determining its three-dimensional structure.

Publishing in *Nature*, EPFL researchers have now uncovered for the first time the 3D structure of $5HT_3$-R, opening the way to understanding other neuroreceptors as well.

Neuroreceptors: structure and function

Communication between the neurons of our body is mediated by

neuroreceptors that are embedded across the cell membrane of each neuron. Neuronal communication begins when a neuron releases a small molecule, called a 'neurotransmitter', onto a neighboring neuron, where it is identified by its specific neuroreceptor and binds to it. The neurotransmitter causes the neuroreceptor to open an electrically conducting channel, which allows the passage of electrical charge across the neuron's membrane. The membrane then becomes electrically conducting for a fraction of a millisecond, generating an electrical pulse that travels across the neuron. The family of neuroreceptors that work in this way is widespread across the nervous system, and is referred to as the "ligand-gated channel" family.

The mystery is how the binding of the neurotransmitter can induce the opening of an electrical channel to transport a signal into the neuron. The understanding of these molecular machines is of great medical importance, especially since neuroreceptors are involved in many neurological diseases. Currently, none of the mammalian ligand-gated channel neuroreceptors have been structurally described, which significantly limits our understanding of their function on a molecular level.

Uncovering the structure of 5HT3-R

The team of Horst Vogel at EPFL has used X-ray crystallography to determine the 3D structure of a representative ligand-gated channel neuroreceptor, the type-3 serotonin receptor ($5HT_3$-R). This neuroreceptor recognizes the neurotransmitter serotonin and opens a transmembrane channel that allows electrical signals to enter certain neurons. The $5HT_3$ receptor was grown in and then isolated from human cell cultures, and finally crystallized.

But before obtaining the 5HT3-R crystals, the EPFL team had to overcome a number of challenges. First, the relatively large size of the

membrane-embedded 5HT3-R, like that of other similar channel neuroreceptors, makes it notoriously difficult to purify in sufficient quality and quantity. After years of painstaking work, the EPFL scientists succeeded in obtaining a few milligrams of $5HT_3$-R, which was still not enough to grow crystals using conventional methods.

Still, the crystal quality was insufficient. To address this, Vogel's team used small antibodies, so-called nanobodies, which were obtained from llamas after the animals were injected with purified $5HT_3$-R. From a large library of isolated nanobodies, a particular one was found to form a stable complex with the $5HT_3$-R, and this complex eventually yielded crystals of exceptional quality.

After this, the procedure was straightforward: The crystals for X-ray crystallography were investigated at the synchrotron facilities at the Paul Scherrer Institut in Villigen and the European facilities in Grenoble. In this well-established technique, the crystals diffract X-rays in a characteristic pattern from which the 3D structure can be reconstructed.

The X-ray diffraction experiments yielded the 3D structure of $5HT_3$-R at an unprecedented resolution of 3.5 Ångstroms. The resulting 3D image shows a bullet-shaped $5HT_3$ receptor with its five subunits symmetrically arranged around a central water-filled channel that traverses the neuron's cell membrane. The channel can adopt two states: a closed, electrically non-conducting state or, after binding a neurotransmitter, an open, electrically conducting state that allows the flow of electrical charges in and out of the neuron to generate an electrical signal.

"We have now elucidated the molecular anatomy of a receptor that plays a central role in neuronal transmission," says Horst Vogel. "It is the first 3D structure of its kind and may serve as a blueprint for the other receptors of this family. In the next step, we have to improve the

resolution of the structure, which might give us information on how to design novel medicines that influence this neuroreceptor's function."

More information: Hassaine G, Deluz C, Grasso L, Wyss R, Tol MB, Hovius R, Graff A, Stahlberg H, Tomizaki T, Desmyter A, Moreau C, Li X-D, Poitevin F, Vogel H, Nury H. X-ray structure of the mouse serotonin 5-HT_3 receptor. *Nature* DOI: 10.1038/nature13552

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