Scientists discover stable intermediate of serotonin receptor

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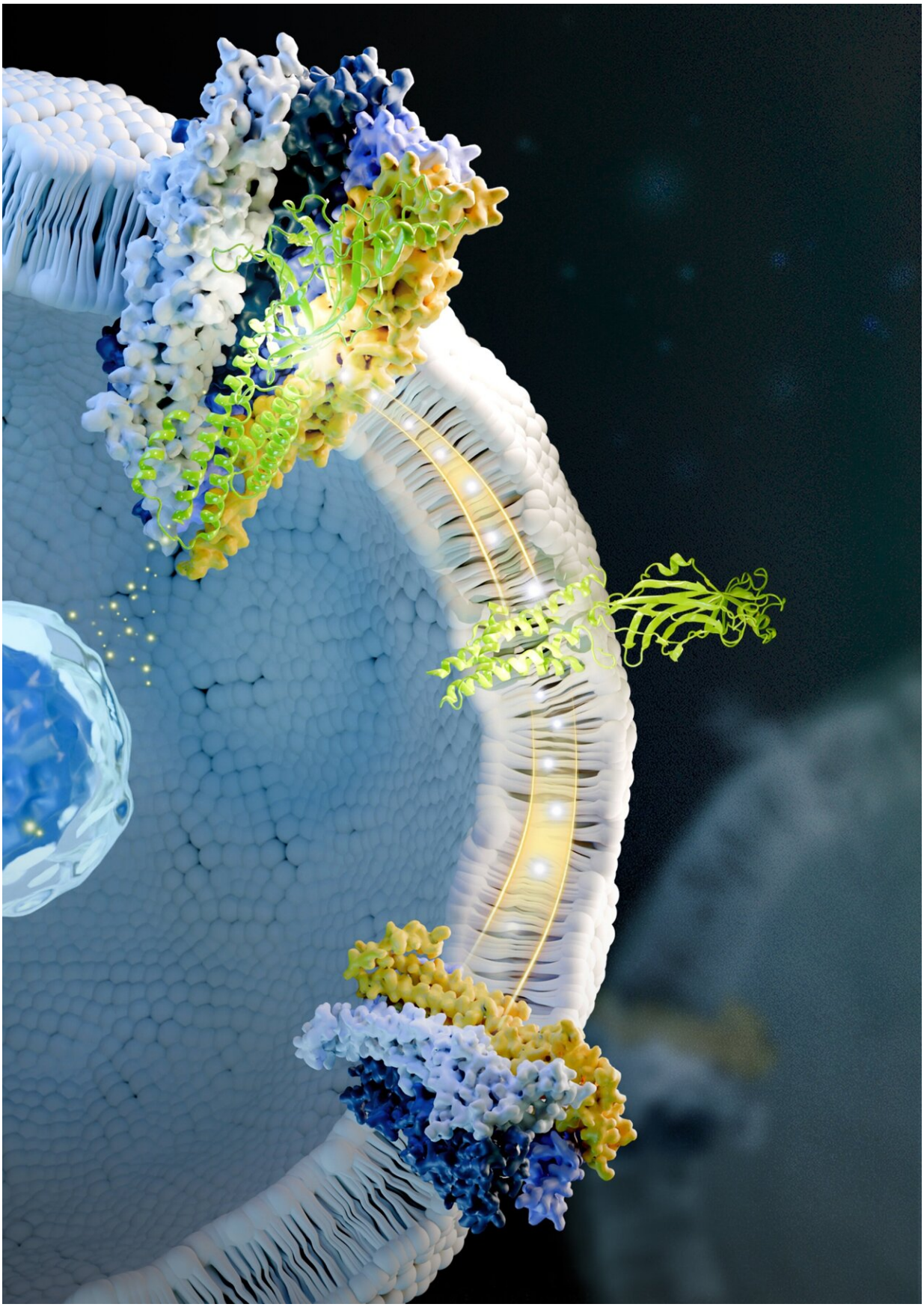

Researchers have identified an intermediate form of the 5-HT3A serotonin receptor (blue). In its final form, a fifth subunit is added (green). The intermediate form presents a potential new drug target.. Credit: Max Delbrück Center

A new study published in *The EMBO Journal* points to new potential strategies to treat psychiatric and gastrointestinal disorders that are not well addressed by current medications. Dr. Bianca Introini and her colleagues in the In Situ Structural Biology lab of Professor Misha Kudryashev have identified a stable intermediate form of the pentameric serotonin-gated 5-HT3A receptor—a cellular membrane protein.

The researchers' ability to identify such a structure is exceptional, says Kudryashev, because intermediates of assembling membrane proteins are notoriously difficult to purify. The intermediate form could serve as a new drug target.

Serotonin is well known as a neurotransmitter that modulates neural activity and a variety of neuropsychological processes. Drugs that target serotonin receptors are used widely in psychiatry and neurology, for example. They are also given to patients to alleviate nausea and vomiting caused by chemotherapy and radiotherapy. However, these drugs often come with side effects that limit their use.

Of the seven known serotonin receptors, 5-HT3A is the only one that is an ion channel—transmembrane pore-forming proteins that act as gatekeepers and allow the flow of selected ions across cellular membranes. Cells with 5HT3A ion channels are found in the brainstem and the gastrointestinal tract. These cells form part of a circuit that

regulates the movement of food through the gut, conveys sensory information, and triggers the gag reflex.

Studying the structure of serotonin receptors

Living cells are surrounded by membranes. Many membranes contain proteins that are involved in transmitting signals and transporting substances across the membranes. Membrane proteins are thus important in maintaining the health of cells, disruptions in their function are associated with many diseases.

Membrane proteins can be multimeric, whereby several copies of the same molecule assemble to form a final functional structure. Synthesis and assembly of multimeric membrane proteins takes place deep within cells, making it challenging to study the intermediates of this process.

For several years, the Kudryashev lab has been investigating at the atomic level, how the serotonin receptor ion channel opens and closes in response to serotonin binding. To study the protein's structure, the research team uses cryo-electron microscopy, a technique that allows imaging of a thin layer of frozen proteins or cells using electrons.

Not the canonical five subunits

While studying the structure of the 5-HT3A receptor, Dr. Introini found that some molecules consisted of four subunits bound in a tetramer complex, instead of the canonical five.

"This was curious," Dr. Introini says, "because Cys-loop receptors are made up of five protein subunits." Five subunits typically assemble into a pentameric complex.

To gain deeper insights into the tetramers' function, the researchers teamed up with scientists from The Research Center for Computer-aided Drug Discovery at the Institute of Biomedicine and Biotechnology in Shenzhen, China. Using computational simulations, they proposed that the tetramer was an intermediate structure that is processed to produce the final pentameric structure.

Interestingly, the tetramers exist in two distinct forms. One carries a partially open extracellular domain that, as shown by molecular dynamics simulation experiments, allows the insertion of the fifth subunit, Kudryashev explains, providing evidence that the tetramer indeed represents an intermediate molecule.

"The publication not only advances our understanding of the synthesis and assembly of these proteins and other multimeric proteins in membranes," says Kudryashev, "it also suggests a potential alternative strategy for regulating serotonin levels in cells by targeting this intermediate protein."

More information: Bianca Introini et al, Structure of tetrameric forms of the serotonin-gated 5-HT3A receptor ion channel, *The EMBO Journal* (2024). DOI: 10.1038/s44318-024-00191-5

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