Study provides structural insights into how cholesterol in the brain regulates ion channels and alters their function

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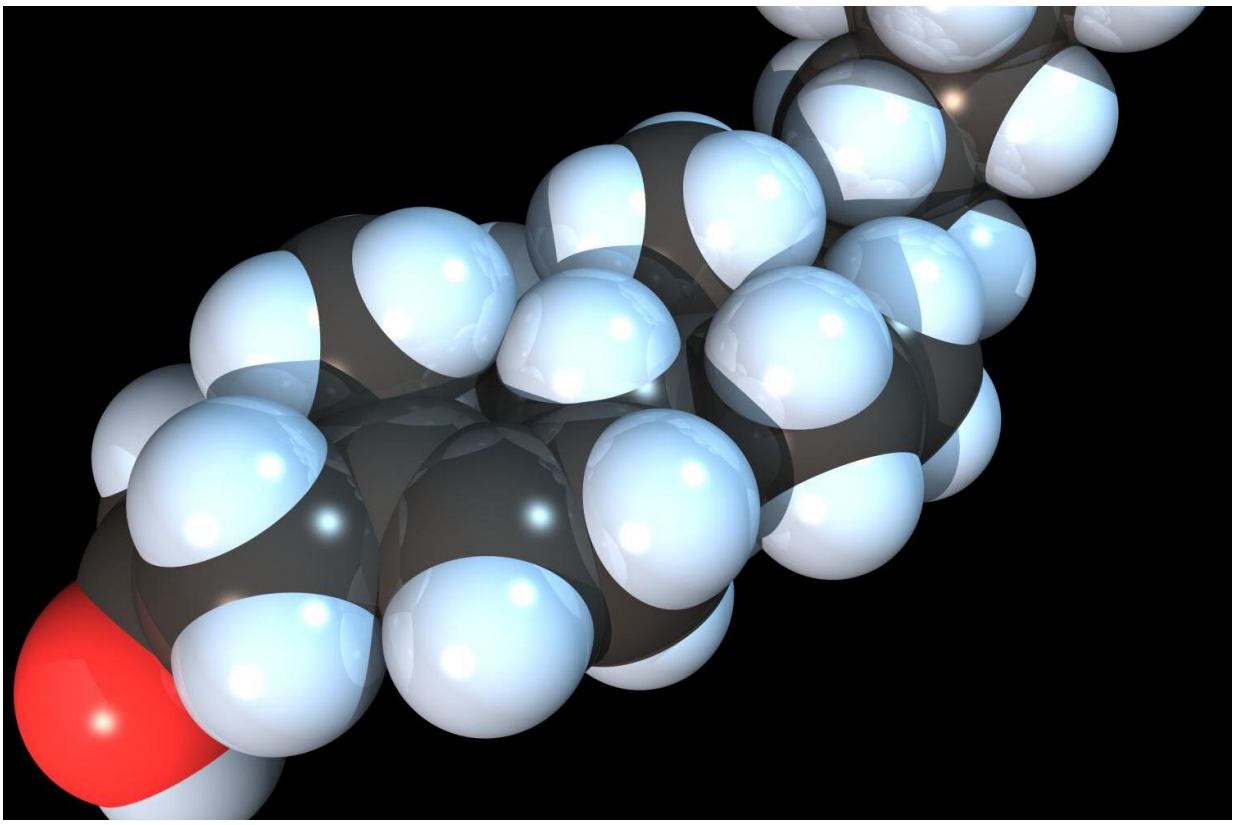

Space-filling model of the Cholesterol molecule. Credit: RedAndr/Wikipedia

Through a structural and functional approach, researchers from the Icahn School of Medicine at Mount Sinai and Stanford University

Medical Center identified physical binding sites for cholesterol in the brain's G-protein-gated inwardly rectifying potassium (GIRK) channels, potassium channels that have been implicated in a variety of neurological disorders. The team provides details on how cholesterol in the brain regulates these ion channels and alters their function, which can aid in drug development and potentially treating neurodegenerative diseases.

The team solved a three-dimensional structure of a GIRK channel that reveals a physical site where cholesterol directly interacts with the channel. In addition, they visualized the GIRK channel in different poses, illustrating how the channel steps through intermediate states before opening and allowing potassium ions to flow through the channel

Our brains contain a lot of cholesterol, which is known to affect the function of brain proteins. Brain cholesterol is also increased in people with Alzheimer's dementia or Parkinson's disease. Ion channels play a fundamental role in nerve cell communication and elevations in cholesterol can increase the activity of these channels, leading to decreased neuronal activity. Findings from this study open the doors for the larger research community to utilize this cholesterol site in the ion channel for drug development and potentially treating neurodegenerative disorders like Alzheimer's and Parkinson's disease.

The team presents structures of the GIRK2 channel in the presence and absence of the cholesterol derivative cholesteryl hemi-succinate (CHS) and a membrane phospholipid (PIP_2). The structures reveal that CHS binds near PIP_2 in lipid-facing hydrophobic pockets of the transmembrane domain.

To better understand the structural basis for cholesterol modulation of GIRK channels, they employed cryogenic electron microscopy to visualize GIRK2 under different conditions

Elevated levels of cholesterol found in some neurodegenerative diseases can affect the function of ion channels. The structural analysis presented in this study suggests that cholesterol can stabilize lipid interactions that promotes engagement of the cytoplasmic region of the channel onto the membrane-spanning region. Mutagenesis of amino acids in the CHS binding pocket eliminates cholesterol-dependent potentiation of GIRK channels, providing functional evidence supporting the three-dimensional structural visualization.

Said Mount Sinai's Dr. Paul Slesinger of the research: "It has been reported that brain cholesterol, which is different from the cholesterol in our blood, is elevated in people with some neurodegenerative diseases. Our study reveals how the physical interaction of brain cholesterol with an ion channel can enhance its activity. Knowing this provides an opportunity to develop drugs that might interfere with this effect of brain cholesterol.

The study is published in *Cell Reports*.

More information: Structural insights into GIRK2 channel modulation by cholesterol and PIP_2, *Cell Reports* (2021).

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