New study sheds light on potassium channels to help researchers design better drugs

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High-resolution cryo-EM structure reveals the AUT5 binding site in Kv3.1. a Overall cryo-EM reconstruction of Kv3.1/AUT5 complex. EM map feature for AUT5 is highlighted in red. b Cartoon representation of AUT5-binding site. Key residues for interaction with AUT5 (dark red) are highlighted as stick representations. Hydrogen bonds and van der Waals contacts are shown as black and orange dashed lines, respectively. The black dashed lines indicate potential
Potassium channels are openings that allow charged potassium atoms to cross the cell membrane. Voltage-gated potassium channels—which open only when a specific voltage is reached across the cell membrane—are essential for the electrical impulses that nerve cells or neurons use to communicate. Dysfunction of these channels is implicated in diseases like epilepsy, autism and schizophrenia.

To treat these conditions, certain voltage-gated potassium channels have become targets for drug developers. Over a decade ago, researchers at Autifony Therapeutics synthesized a molecule called AUT5, which helps certain voltage-gated potassium channels stay open. But its mechanism of action was unknown, making it difficult to develop AUT5 into an effective, specific, and safe drug.

To learn how AUT5 binds to potassium channels, neuroscientist Manuel Covarrubias, MD, Ph.D. and his research assistant Qiansheng Liang, MD led a study published in Nature Communications that focused on Kv3 channels, the subclass of voltage-gated potassium channels that selectively bind AUT5. They are connected to multiple neurological diseases.
Through a multi-prong process involving electrophysiology, **structural biology** and cryo-**electron microscopy**, a technique that allows direct visualization of membrane proteins at near-atomic resolution, Dr. Covarrubias' lab and global collaborators identified a "pocket" in Kv3 as the **binding site** for AUT5. This pocket is situated between the channel's voltage sensor and the opening that potassium travels through, and next to a region known as the "extracellular turret," named for its resemblance to a tower projecting above a castle. The structure of the extracellular turret is such that it helps secure the binding of AUT5, like a well-fitting glove.

"When we started, we knew what AUT5, the 'hand,' looked like, but we didn't know what or where the 'glove,' the binding site, was," says Dr. Covarrubias. "Now, we know the shape of the glove, and how it wrinkles to keep the Kv3 pore open."

This research will help drug companies develop even more effective compounds to treat potassium channel-related diseases. Clinical trials using AUT5 and closely related compounds are already underway to treat children with intractable epilepsy and fragile X syndrome.

**More information:** Qiansheng Liang et al, The binding and mechanism of a positive allosteric modulator of Kv3 channels, *Nature Communications* (2024). [DOI: 10.1038/s41467-024-46813-8](https://doi.org/10.1038/s41467-024-46813-8)

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