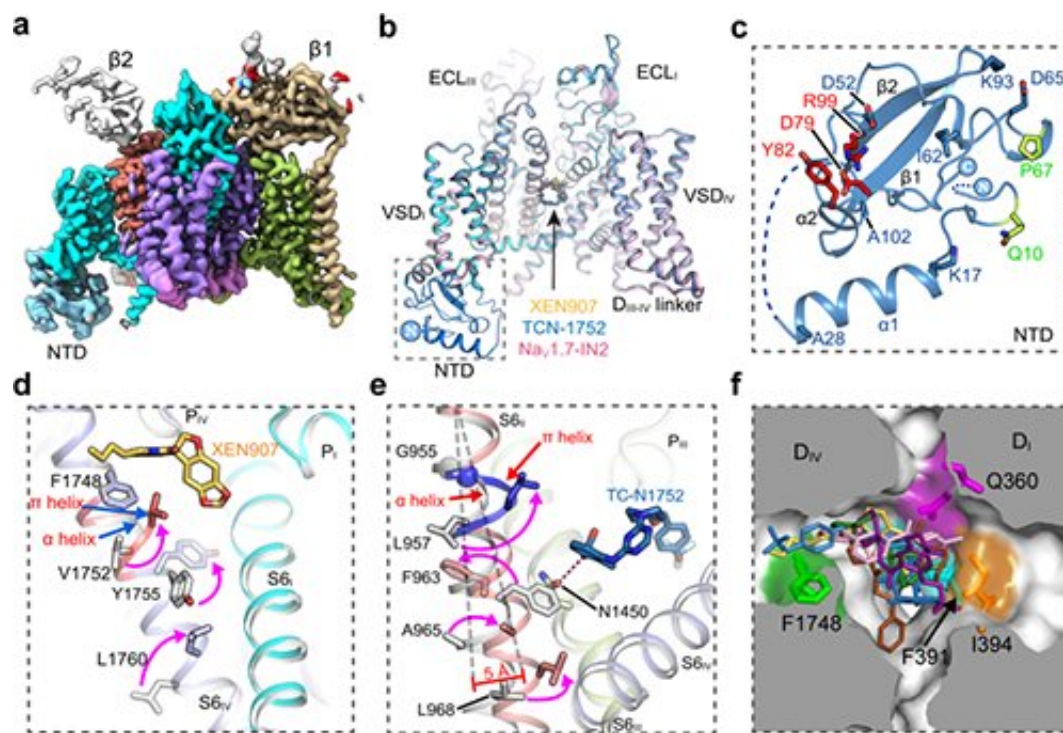


Scientists provide structural insights into NaV1.7 modulation by inhibitors, to block pain signals to the brain

November 28 2022, by Zhang Nannan



a. Cryo-EM map of Na_v1.7; b. Cartoon representation of Na_v1.7 in complex with inhibitors; c. The structure of NTD; d. XEN907 binding site; e. TC-N1752 binding site; f. Superposition of inhibitors in the central cavity of Na_v channel. Credit: Institute of Physics

Chronic pain is an extremely common condition that affects about 20% of the general population. Given the shortage of effective and non-

addictive analgesics, new anti-pain drugs are eagerly awaited. Voltage-gated sodium channel Na_v1.7 plays an essential role in the transmission of pain signals to the brain, and multiple mutations in Na_v1.7 have been directly linked to a variety of human pain disorders.

The blockade of Na_v1.7 can inhibit pain sensation; thus, it represents an attractive target for potential non-addictive analgesics. However, Na_v1.7 is a very challenging target for developing selective candidate drugs, partially owing to the high sequence similarity within the nine NaV [channel](#) isoforms.

Understanding the structural discriminations among NaV channel isoforms and the mechanism of how these inhibitors regulate Na_v1.7 functions can support Na_v1.7-related drug development. Zhang Jiangtao in Prof. Jiang Daohua's group from the Institute of Physics of the Chinese Academy of Sciences has reported on the cryo-EM structures of Na_v1.7 in complex with three pore blockers, providing mechanistic insights into Na_v1.7 modulation by pore blockers.

The researchers solved high-resolution cryo-EM structures of Na_v1.7 complexed with three chemically distinct small molecule inhibitors XEN907, TCN-1752, and Na_v1.7-IN2, respectively.

The structure revealed the previously unresolved N-terminus domain (NTD) of Na_v1.7, explaining that the conserved NTD is critical for NaV channel function.

In addition, the structures confirmed that the central cavity of Na_v1.7 accommodates multiple [drug](#) binding sites, which can directly block the channel. Two of the three inhibitors also caused local conformational rearrangements of the S6 helix, that further affect the channel function.

The XEN907 caused a α -helix to the π -helix transition in S6_{IV} of

Na_v1.7, which significantly slowed down the recovery of Na_v1.7 from fast inactivation. The binding of TC-N1752 indirectly caused a local shift from the α -helix to the π -helix in S6_{II} of Na_v1.7, and shifted the S6_{II} helix approximately 5 Å toward the activation gate, leading to a completely closed activation gate, and stabilizing Na_v1.7 in the inactivated state.

Further [structural analysis](#) revealed that the inhibitor binding sites located in the central cavity are highly conserved among the nine Na_v channel isoforms. Therefore, it is very challenging to achieve subtype-selective drugs binding in the central cavity of Na_v channels.

This study suggests that future efforts on searching for Na_v1.7-selective [inhibitors](#) should focus on the regions that are relatively less conserved, such as the voltage-sensing domain.

This study, titled "Structural basis for Na_v1.7 inhibition by pore blockers," was published in *Nature Structural & Molecular Biology*.

More information: Jiangtao Zhang et al, Structural basis for Na_v1.7 inhibition by pore blockers, *Nature Structural & Molecular Biology* (2022). [DOI: 10.1038/s41594-022-00860-1](https://doi.org/10.1038/s41594-022-00860-1)

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