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

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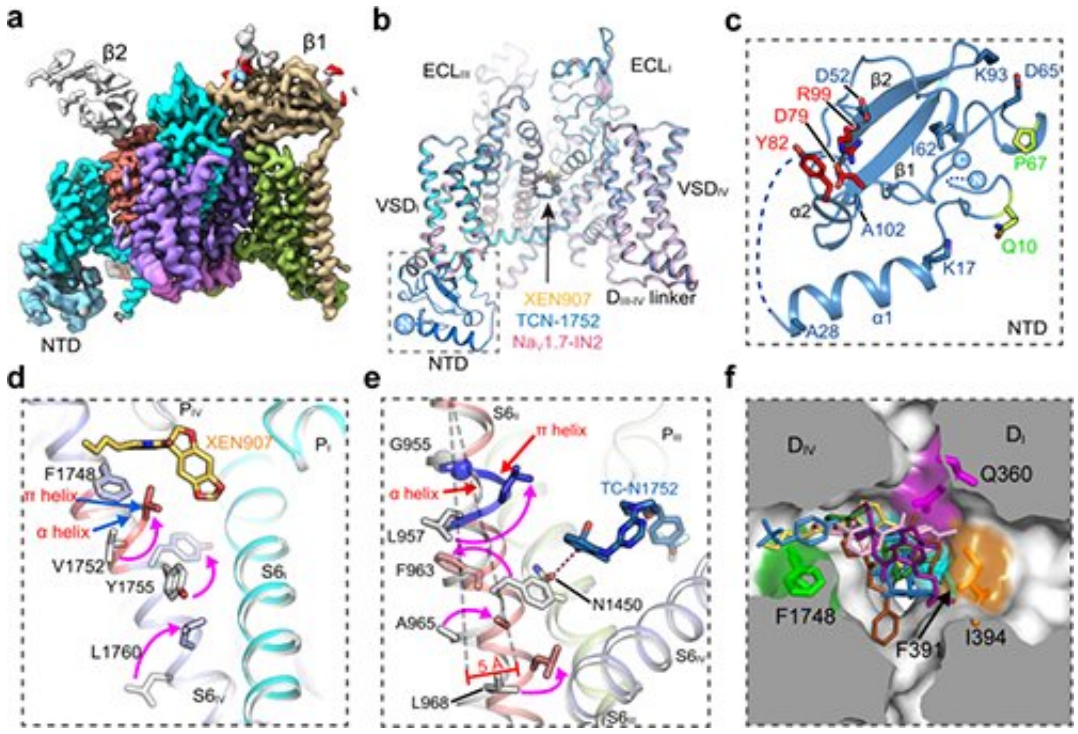

a. Cryo-EM map of $Na_V1.7$; b. Cartoon representation of $Na_V1.7$ in complex with inhibitors; c. The structure of NTD; d. XEN907 binding site; e. TC-N1752 binding site; f. Superposition of inhibitors in the central cavity of Na_V channel. Credit: Institute of Physics

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

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