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Modeling the Binding of Tetrodotoxin and Saxitoxin to the Nav1.7 Voltage-Gated Sodium Channel

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PDB File: 6J8J tetrodotoxin (TTX) Y1755 down & 6J8H saxitoxin (STX) Y1755 down

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Huaizong, Shen et al. Structures of human Nav1.7 channel in complex with auxiliary subunits and animal toxins. Science 363: 1303-1308 (2019). https://doi.org/10.1126/science.aaw2493

Description:

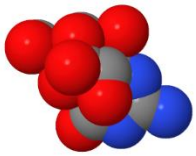
Throughout the world, staggering amounts of individuals suffer from chronic pain (persistent pain exceeding three months), as well as its burdens and ramifications, which include worsening of chronic disease, psychiatric disorders, and quality of life. Approximately 1.5 billion people suffer from chronic pain worldwide, with 68 million suffering within the United States alone. In individuals with cancer, chronic pain is a common long-term effect. Within the U.S., nearly 5.5 million cancer survivors experience chronic pain, displaying a rate that is double that of the general population. Approximately 20% of cancer pains have neuropathic origins and develop as a direct result of chemotherapy and radiation-based treatments.

While there are a variety of medicines that seek to lessen pain, drugs that block the sodium voltage channels are especially promising. Such drugs have been modified from naturally occurring toxins found in pufferfish. Halneuron, a new drug currently in development, seeks to provide pain relief to those suffering from chemotherapy-induced neuropathic pain. This drug includes Tetrodotoxin (TTX) as its main active ingredient. Tetrodotoxin, a potent neurotoxin and small molecule most found in most species of pufferfish, works as a pore blocker within the Nav1.7 voltage-gated sodium channel to limit and reduce pain signal conduction. Our model showcases the structural details of Tetrodotoxin (TTX) $C_{11}H_{17}N_3O_8$ as a pore blocker within this channel, providing insight into its use as an analgesic. Furthermore, our model highlights the slight structural differences between Tetrodotoxin (TTX) and a very similar toxin, Saxitoxin (STX) $C_{10}H_{17}N_7O_4$. While TTX is a poison produced by pufferfish, STX is a toxin produced by algae and concentrated in mussels and other shellfish (and fish) causing paralytic shellfish poisoning. STX has less binding affinity than TTX for the receptor. Both toxins are being investigated for their ability to block the sodium channel leading to the inhibition of pain. A comparison of how these two toxins function as pore blockers within the Nav1.7 channel can allow for further insight into their analgesic efficacy in relation to one another.

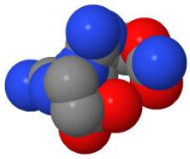
Plan:
STX and TTX bind to the Nav1.7 channel pore domain with the use of magnets. Parts of the channel receptor that are important in binding both toxins, as well as the amino acids that are unique to each toxin, are highlighted.

Specific Model Details:

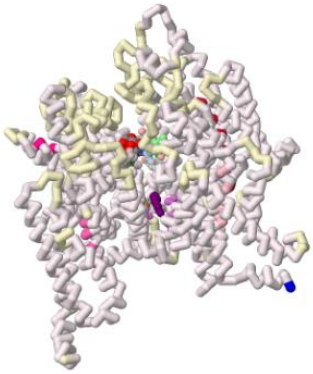
TTX



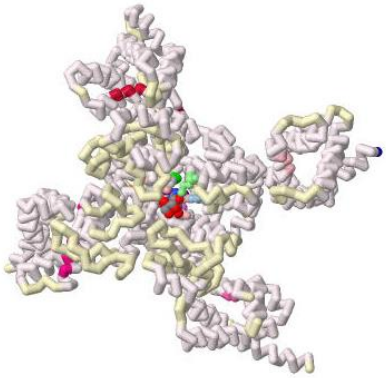
STX



Nav1.7 Labeled Side View



Nav1.7 Labeled Top View



General:

The alpha subunit of the Nav1.7 channel is shown; the backbone is highlighted in lemon chiffon; the alpha helices are colored lightcyan. The N and C terminals are marked in blue and red respectively and are both found inside the cell while the voltage sensing domains are found in the membrane. The helix 4 (S4) of each of the Voltage sensing domains have their positively charged lysine or arginine residues highlighted in increasingly dark shades of pink. (VSD I is the lightest pink, VSD IV is the darkest red). Amino acids in the Nav1.7 receptor that bind to both STX and TTX are shown in spacefill and light cpk colors: Tyr362, Glu364, Arg922, Glu927, Glu930, Thr1409. Amino acids in the Nav1.7 receptor that bind to TTX but not STX are highlighted medium turquoise on the backbone: Gly1407, Gly1699, Phe1405, Ala1698. Amino acids in the Nav1.7 receptor that bind to STX but not TTX are highlighted aquamarine on the backbone: Trp1700, Asp1744. The DEKA motif (Asp361, Glu930, Lys1406, and Ala1698) is highlighted in shades of green (Asp is lime, Glu is pale green, Lys is dark olive green, Ala is dark sea green) on the backbone. **Lys 1406 is the critical determinant that specifies the selective permeability of sodium over potassium in these voltage gated channels.** The linker in between segments III-IV contains the fast inactivation motif Ile1472, Phe 1473, Met 1471 and the backbone is colored orange. **This helps to regulate the firing frequency of the action potentials within this channel.** There are 4 hydrophobic residues of note on the locus of the S6 of VSD IV and these are Leu398, Leu964, Ile1453, and Tyr1755. These residues are noted by sidechains in light purple (orchid) with the Tyrosine in darker purple. **The tyrosine forms an up or down confirmation (down here) allowing sodium ions to be pushed through the channel.**

Amino acids binding to STX and TTX	**Tyr362**	**Glu364**	**Glu930**	**Glu927**	**Arg922**	**Thr1409**
Amino acids binding to STX	**Trp1700**			**Asp1744**		
Amino acids binding to TTX	**Gly1407**		**Gly1699**	**Phe1405**	**Ala1698**	
DEKA motif	**Asp361**		**Glu930**	**Lys1406**	**Ala1698**	
Fast inactivation motif	**Ile1472**		**Phe 1473**		**Met 1471**	
4 hydrophobic residues - S6 locus VSD IV	**Leu398**		**Leu964**	**Ile1453**	**Tyr1755**	

Figure 1: Identified amino acids that interact with STX and TTX by visiting protein databank and selecting ligand interactions. We found the list of amino acids binding to the ligands that were in common between STX 6J8H and TTX 6J8J; note that you must use the auth a chain numbers which are listed second. Note that one of the members of DEKA motif, Glu930, is also one of the amino acids that binds to both TTX and STX. This residue is shown in green instead of cpk. DEKA member and amino acid, Ala1698, binds to TTX as well.