NATIONAL CENTER FOR CASE STUDY TEACHING IN SCIENCE

Epilepsy-Causing Mutations:

The Importance of Protein Structure to Function

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Jessie loved learning new things in her biology courses at college. Recently, she had learned about how neurons signal to each other and how that signaling underlies all human behavior and activity. Neurons, like all cells, have a plasma membrane that only allows certain solutes and molecules to cross. Ions like sodium and potassium ions are unevenly distributed on both sides of the membrane, and they need a pore or channel in the membrane to be able to cross the membrane. These pores or channels are formed by proteins. Neurons have a variety of pores, channels, and signal receptors that they use to communicate with each other.

Neurons use small signaling molecules to signal to each other, and the signals cause ions to move across the membrane. The movement of ions across the membrane can activate a voltage-gated channel. One such channel is called Kv7.2, a voltage-gated potassium channel. Kv7.2 is a tetramer, meaning it is made up of four subunits. When this channel is activated, the protein changes shape (called a conformational change) and allows potassium ions to leave the neuron. Normally, Kv7.2 prevents neurons from being overexcited, which would lead to excessive signaling between neurons. Below is the ribbon structure of the voltage-gated potassium channel (Kv7.2).

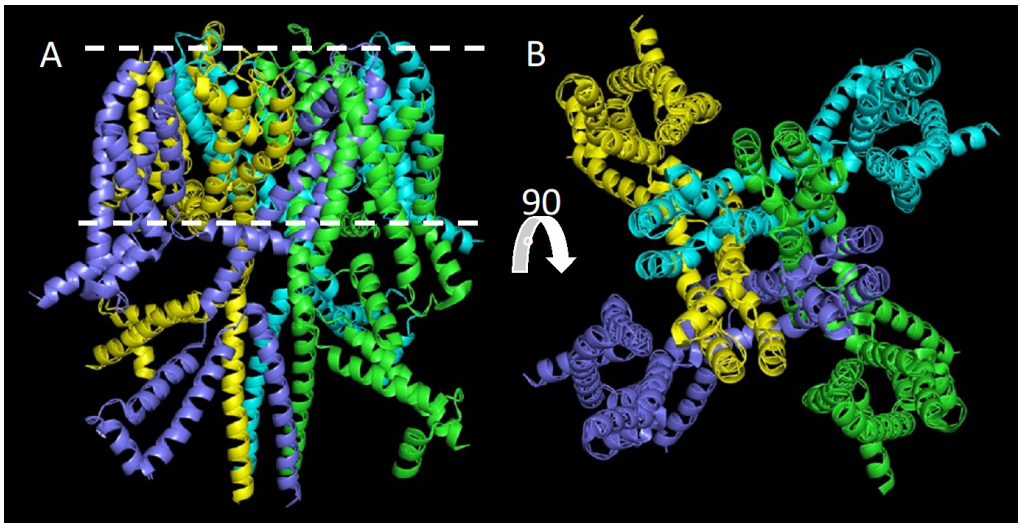

Figure 1. The voltage-gated potassium channel (Kv7.2) structure was solved using cryo-electron microscopy. (A) Kv7.2 looking at the side view of the channel. The dashed lines indicate the bounds of the lipid bilayer, and the portion of the protein below the lipid bilayer is inside the cell (intracellular). (B) The channel is rotated 90 degrees to look at it as if from the extracellular side and trying to see the pore where potassium passes through. This structure captured the inactive or closed-pore state of the channel. (Li et al., 2021) *Source:* Figure created using Pymol software. The protein structure is PDBID 7CR0 and was accessed from the RCSB Protein Data Bank <https://www.rcsb.org/>.

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Questions

1. In her research, Jessie finds that Kv7.2 is an integral membrane protein found in neurons. What does it mean for a protein to be an integral membrane protein?

2. Jessie has just learned about how protein structure is hierarchical, and there are four possible levels of structure. List and define the four levels of protein structure.

3. Kv7.2 has four subunits, indicated by the four colors in Figure 1 above (green, gold, purple, and cyan). What is the highest level of protein structure that Kv7.2 has, since it has different subunits combining together?

4. What types of bonds can hold together tertiary and quaternary structure of a protein?

5. Each subunit of Kv7.2 has about 850 amino acids (the number depends on the version of the gene used). Which level of protein structure does that statement describe?

6. What type of bond connects each amino acid to the adjacent amino acid in the protein?

7. Draw the structure of an ionized amino acid with R for the side chain. Circle the functional groups where bonds can be made with other amino acids to form the primary structure of a protein.

8. What secondary structure element do the spiral ribbons indicate the channel has?

As Jessie learned more about Kv7.2, she came across studies that have shown that certain mutations in Kv7.2 cause epilepsy. She turned to the World Health Organization (WHO) website to learn more about epilepsy (https://www.who.int/health-topics/epilepsy). Epilepsy is a condition whereby individuals suffer from seizures, which are episodes with uncontrolled muscle movement in specific regions of the body or the whole body. Jessie learned that epilepsy affects 50 million people around the world. She consulted her biology textbook and realized that mutations can result in different amino acids being included in a protein.

Question

9. What three categories can amino acid R groups be classified into based on their chemical properties?

One of the mutations in Kv7.2 that causes epilepsy is a replacement of a tryptophan (W) to an arginine (R) at amino acid 344 (notated as W344R) (Urrutia et al., 2021). Jessie has learned that tryptophan has a large, hydrophobic side chain while arginine has a positively charged side chain. The structures of tryptophan and arginine are shown in Figure 2.

Questions

10. What type of interactions can the tryptophan side chain form to help form protein tertiary structure?

11. How do interactions that the arginine side chain can form as part of tertiary structure differ from tryptophan?

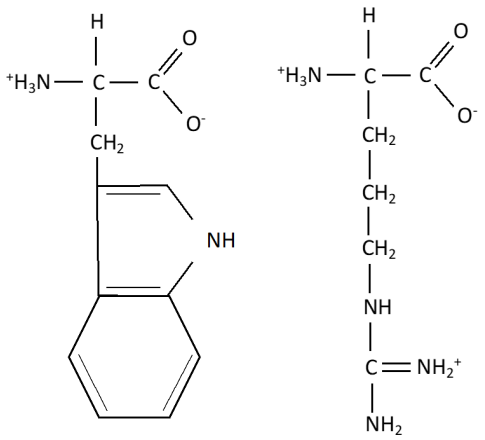

Figure 2. Tryptophan (left) and arginine (right).

Jessie was fascinated by Kv7.2 and soon discovered that Kv7.2 normally binds to another protein, called calmodulin, on its intracellular side. Calmodulin is a common protein in neurons and helps regulate the activity of ion channels. Jessie wondered if calmodulin binding is prevented when Kv7.2 has the W344R mutation.

Questions

12. Jessie searched published studies to help answer her question and found that the W344R mutation does not affect Kv7.2's ability to bind to calmodulin. However, studies have shown that the channel's subunits cannot assemble properly when they have the W344R mutation (Urrutia et al., 2021). Propose an explanation for why the protein cannot fold properly.

13. Why does the W344R mutation in Kv7.2 cause epilepsy?

References

Li, X., Q. Zhang, P. Guo, J. Fu, L. Mei, D. LV, J. Wang, D. Lai, S. Ye, H. Yang, & J. Guo. (2021). Molecular basis for ligand activation of the human KCNQ2 channel. *Cell Research* 31(1): 52–61. <https://doi.org/10.1038/s41422-020-00410-8>

Urrutia, J., A. Aguado, C. Gomis-Perez, A. Muguruza-Montero, O.R. Ballesteros, J. Zhang, E. Nuñez, C. Malo, H.J. Chung, A. Leonardo, A. Bergara, & A. Villarroel. (2021). An epilepsy-causing mutation leads to co-translational misfolding of the Kv7.2 channel. *BMC Biology* 19, 109. <https://doi.org/10.1186/s12915-021-01040-1>