2016-2017
Research and Design Model

Cudahy High School SMART Team

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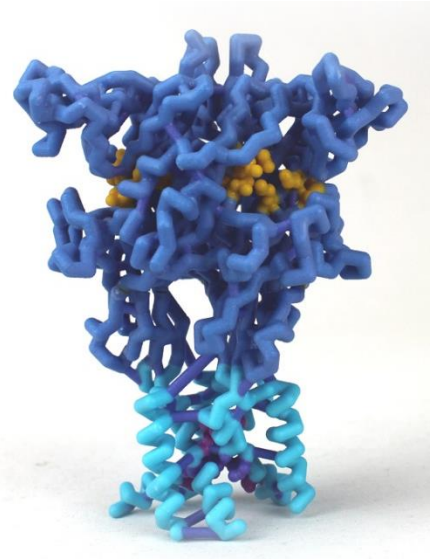
The Ouchless Kind: The Role of P2X4 receptors in Pain Signaling

PDB File: 3i5D



Primary Citation:
Kawate, T., Michel, J. C., Birdsong, W., Gouaux, E. (2009). Crystal structure of the ATP-gated $P2X_4$ ion channel in the closed state. *Nature* 460: 592-598.

Format: Alpha carbon backbone
RP: Zcorp with plaster

Description: According to Apfelbaum et al., (2003), 80% of patients experience acute pain after surgery where opiates are most commonly prescribed to alleviate this pain. Twenty-five percent of these postoperative patients experience adverse side effects related to opiates, including increased pain, addiction, and itching. To prevent these side effects, researchers are looking into localized treatment for pain, targeting peripheral ion channels instead of targeting the whole central nervous system. The ion channel P2X4 in microglia has been shown to be involved in pain perception after spinal nerve injury, aiding in the transmission of pain signals to the brain by initiating the signaling processes in cutaneous sensory neurons indicating nerve and/or tissue damage. P2X4 is a two-domain ATP-gated channel: the transmembrane domain comprising the channel and the extracellular domain containing the potential ATP binding region. ATP binding, potentially occurring in the groove between the three set of subunits A and B, involving Lys70, Lys72, Phe188, Thr189, Asn296, Phe297, Arg298, Lys316, is required for activation. Once bound, ATP causes a conformational change in the transmembrane portion, opening the channel at Gly350 causing movement at Leu340, Gly343, and Ala344, modeled by the Cudahy SMART (Students Modeling A Research Topic) Team using 3D printing technology. The open channel allows an influx of positive ions into the neuron, resulting in depolarization and the transmission of pain. Therefore, it may be more effective to inhibit P2X4 at the site of pain, such as the incision site, with targeted topical analgesics, instead of systemically treating pain.

Secondary citations:

Apfelbaum, J. L., Chen, C., Mehta, S. S., Gan, T. J. (2003). Postoperative Pain Experience: Results from a National Survey Suggest Postoperative Pain Continues to Be Undermanaged. *Anesthesia & Analgesia* 97(2): 534-540.

Hattori, M., Gouaux, E. (2012). Molecular mechanism of ATP binding and ion channel activation in P2X receptors. *Nature* 485: 207-213.

Tsuda, M. Shigemoto-Mogami, Y., Koizumi, S., Mizokahi, A., Kohsaka, S., Salter, M., Inoue, K. (2003). $P2X_4$ receptors induced in spinal microglia gate tactile allodynia after nerve injury. *Nature* 424: 778-783.

Specific Model Information:

Divisions of the protein

- Extracellular portion contains the ATP binding region – Steel Blue
- Transmembrane portion contains the gate and channel – Cyan

Potential ATP binding region is hypothesized to be comprised of specific amino acids

- Lys70, Lys72, Phe188, Thr189, Asn296, Phe297, Arg298, Lys316 – Gold

Transmembrane stabilizers hold the alpha helices of the gate closed when not active

- Leu346, Ala347 – Slate Blue

Gate allows positive ions to enter the neuron, depolarizing it

- Gly343, and Ala344 – Orchid

Leu350 – Magenta

- Both stabilize the transmembrane portion and is part of the gate

Gate hinge changes position when ATP binds to open the channel

- Gly350– Purple

Struts – Royal Blue

Hydrogen bonds – match the section