PROBING CAPSAICIN-TRPA1 INTERACTIONS WITH COMPUTATIONAL ANALYSIS

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A. PURPOSE

TRPA1 has the potential to serve as a therapeutic target for pain and other disorders. In this pilot study, we implemented molecular docking as a tool to explore the binding affinity of TRPA1 for different capsaicinoids.

B. BACKGROUND

Capsaicinoids are a structurally related group of alkaloid plant secondary metabolites that confer a pungent taste to chilis. Capsaicin is a recognized agonist of the transient receptor potential vanilloid 1 channel (TRPV1) and recent findings support a capacity for activation of the transient receptor potential ankyrin1 (TRPA1) channel. Capsaicin is used as a topical analgesic treatment because of its ability to produce sensory desensitization[5,6]. While the effect of capsaicin on pain has been studied on TRP channels, the comparative binding affinities of capsaicin and its analogs with TRPA1 are not well characterized[7].

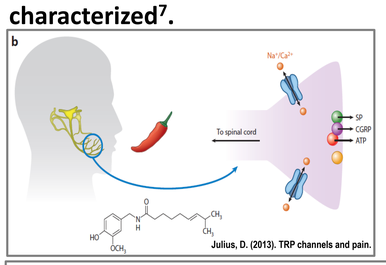

Figure 1: Capsaicin elicits acute pain and neurogenic inflammation by selectively activating excitatory TRP ion channels on nociceptor nerve endings.

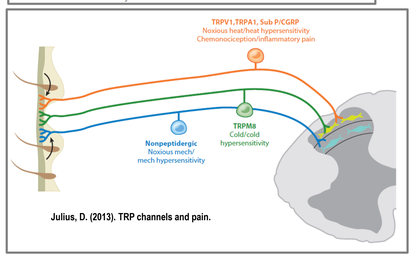

Figure 2: Transient receptor potential channels define functionally distinct nociceptor populations.

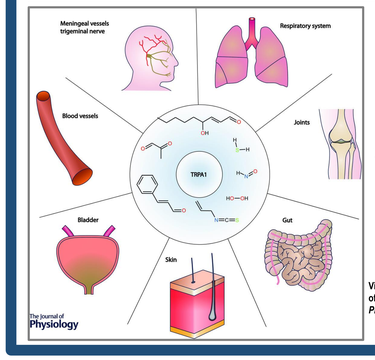

Figure 3: Expression tissue of TRPA1 channel.

Viana, F. (2016). TRPA1 channels: molecular sentinels of cellular stress and tissue damage. *The Journal Of Physiology, 594*(15), 4151-4169. doi:10.1113/jp270935

C. COMPUTATIONAL MODELING

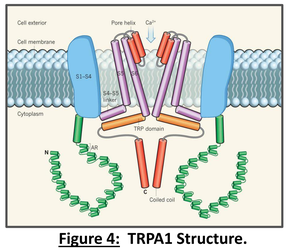

Figure 4: TRPA1 Structure.

Clapham, D. (2015). Pain-sensing TRPA1 channel resolved. *Nature, 520*(7548), 439-441. doi:10.1038/nature14383

Molecular docking is a tool that combines molecular biology and computer-assisted ligand-receptor molecular interactions, and it's used for drug development strategies, with the objective of predict the affinity of a ligand with a 3D representation of the structure.

Molecular docking is used to analyze a large number of ligands, score the results, and guide the optimization of drug design[10].

D . COMPUTATIONAL PIPELINE

1. Install and configure software.

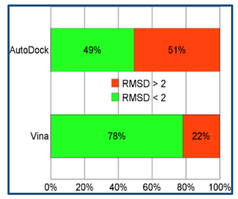

Figure 5: Estimated binding Mode prediction accuracy on AutoDock and AutoDock Vina.

AutoDock Vina - molecular docking and virtual screening program. (2019). *Vina.scripps.edu.*

Figure 6: A. Linux Mint Operating system. B. Marvin Sketch. C. UCSF Chimera.

2. Launch MarvinsSketch; Initiate docking preparation process.

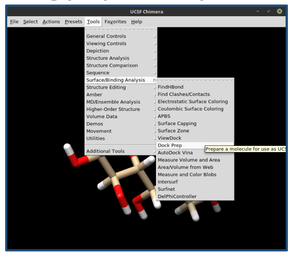

Figure 7: Docking Preparation process for Surface/Binding Analysis in UCSF Chimera.

3. Download or fetch receptor.

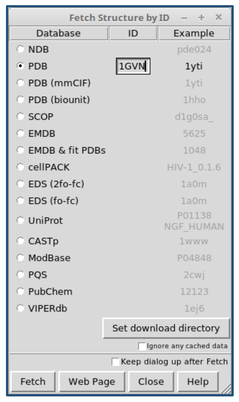

Figure 8: Download or fetch the receptor using the RCSB PDB data base.

4. Select binding area.

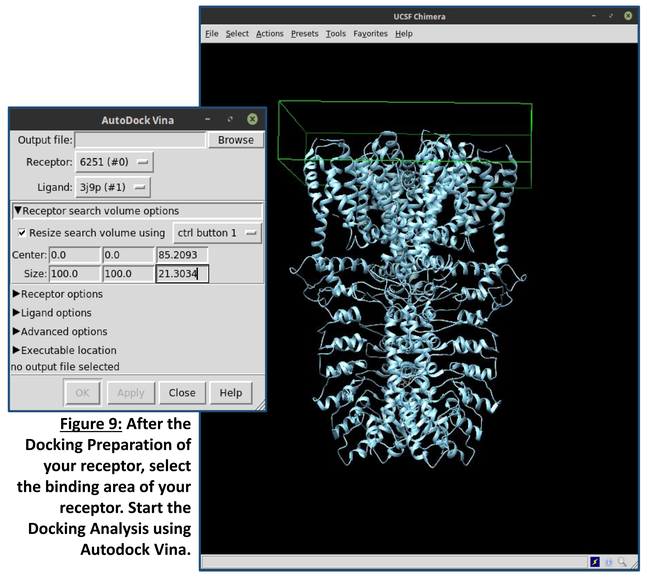

Figure 9: After the Docking Preparation of your receptor, select the binding area of your receptor. Start the Docking Analysis using Autodock Vina.

5. Analyze docking results.

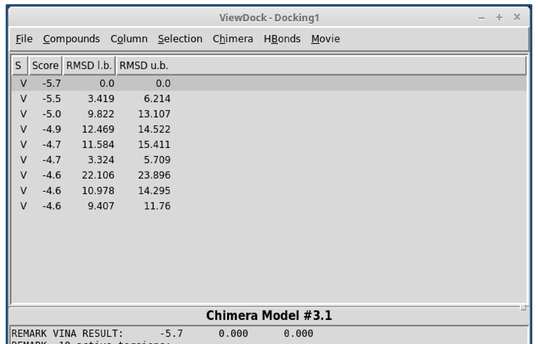

Figure 10: Analyze docking results. Make Replications. Use Autodock Vina for 100% Search of Exhaustiveness.

In the capsaicinoid family series, Zucapsaicin emerged as the highest affinity ligand.

E. DISCUSSION

Analysis was undertaken with the TRPA1 ion channel structure as determined by electron cryomicroscopy (PDB: 3J9P) and the molecular docking of eight capsaicinoids. Binding affinity is an estimation of the intermolecular interactions and the power of the protein-ligand compound[11].

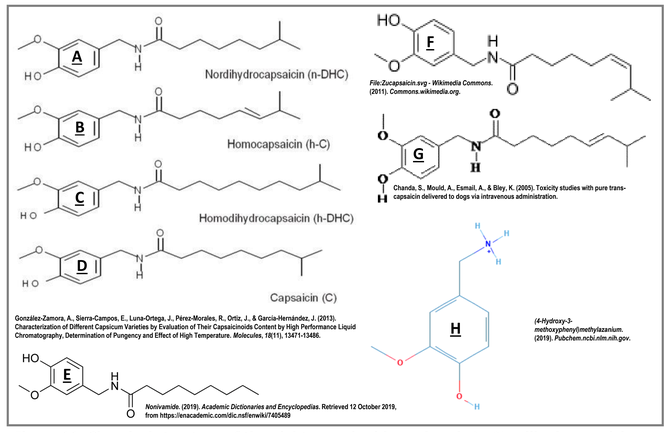

Figure 11: Chemical structure of the eight capsainoids analyzed: A.- Nordihydocapsaicin, B.- Homocapsaicin, C.- Homohydrocapsaicin, D.- Capsaicin, E.- Nonivamide, F.- Zucapsaicin, G.- Trans-capsaicin, H.- Capsaicin Precursor

LIGAND	BINDING ENERGY
CAPSAICIN	-6.1
CAPSAICIN PREC	-5.8
HOMOCAPSAICIN	-6
HOMOHYDROCAPSAICIN	-5.5
MANNITOL	-4.6
NONIVAMIDE	-5.7
NORHYDROCAPSAICIN	-5.7
TRANSCAPSAICIN	-6.2
ZUCAPSAICIN	-6.5

Table 1: Computed Binding Energy of the Ligands.

Molecular simulation studies may help guide the selection and design of capsaicin derivatives for therapeutic purposes. The molecular docking analysis uncovered a high affinity of the TRPA1 channel to Zucapsaicin. Zucapsaicin is currently used in Canada to reduce neuropathic pain and recover articular function, but it is not the first-line of analgesic treatment. The obtained results can guide the design of experiments that evaluate TRPA1 responses to capsaicinoids in cells of the nervous system.

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