Sumatriptan: Engineering Selectivity to 5-HT$_{1B}$ for Migraine Treatment

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Abstract

Sumatriptan is an anti-migraine medication found in the triptan class of drugs. All triptans are associated with an adverse side effect nicknamed the “triptan sensation”.[1] A feeling of tightness or pressure experienced at the face, limbs, and/or chest. Sumatriptan is an agonist for the serotonin receptors 5-hydroxytriptamine (5-HT)$_{1B}$ and 5-HT$_{1D}$.[2] In a clinical trial with a pure 5-HT$_{1D}$ agonist, it was seen that no clinical effect of migraine relief occurred, yet chest constriction still occurred in a handful of patients.[3] We hypothesize that if a pure 5-HT$_{1B}$ agonist could be created, the adverse effect could potentially be eliminated while maintaining the clinical outcome of migraine relief.

Introduction

A 20 year old female patient was prescribed oral sumatriptan tablets to help treat her chronic migraines. She was not informed about any of the possible side effects of the medication, including the “triptan sensation”. Upon taking the drug, she did experience tightness in her chest and throat that continued to worsen. Due to her troubled breathing and lack of knowledge as to what was going on, the patient eventually experienced an anxiety attack. Upon consulting with her physician, she decided that the benefits of the triptan did not outweigh its side effects.

In humans, the neurotransmitter serotonin is found in the gastrointestinal tract, the platelets, and in the central nervous system.[2] It has many functions that are dependent on its location in the body. An imbalance of serotonin in the brain is thought to be the main cause of migraines. In the brain, serotonin works by causing vasoconstriction of the blood vessels. When a person develops a migraine, it is hypothesized that the vessels in their brain dilate causing pain. Thus sumatriptan was created to mimic our endogenous serotonin and is an agonist.

Because sumatriptan and serotonin hit receptors that are not located solely in the brain, it can have off target effects that are not ideal. Vasoconstriction can also occur in the lungs when taking triptans. This adverse reaction is rare, but it is unpleasant and frightening for a patient already suffering from a debilitating migraine.

Molecular Story

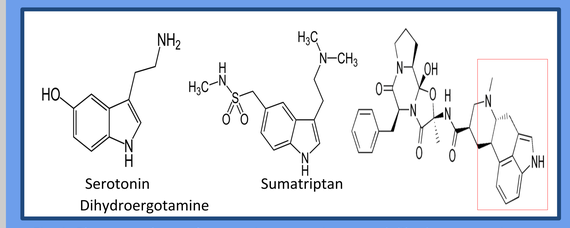


Fig. 1: Pharmacophore of serotonin, sumatriptan, and dihydroergotamine. Serotonin portion of dihydroergotamine is boxed in red.

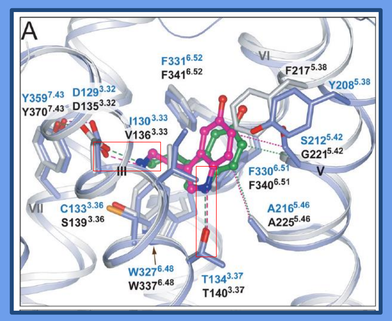


Fig. 2: Serotonin bound to 5-HT$_{1B}$ (light blue) and 5-HT$_{2B}$ (black) receptors. Navy blue represents nitrogen, red is oxygen, and pink/green represents the indole ring. Polar bonding at amino acids D129 and T134 boxed in red.[4]

Dihydroergotamine bound to 5-HT$_{1B}$

- No crystallization of Sumatriptan bound to 5-HT$_{1B}$ has been created, but Dihydroergotamine has been crystallized. (Figure 3)
- The same Serotonin pharmacophore binding can be seen with Dihydroergotamine as seen in Figure 2. (Figure 4)

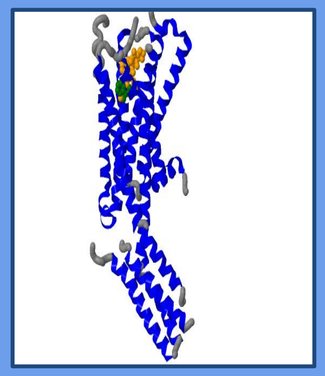


Fig. 3: Dihydroergotamine bound to 5-HT$_{1B}$ receptor. Serotonin pharmacophore of dihydroergotamine is highlighted in green.

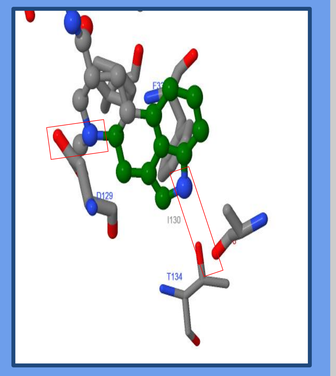


Fig. 4: Expanded view of dihydroergotamine bound to 5-HT$_{1B}$. Serotonin portion of drug highlighted in green. Amino acid binding at D129 and T134 boxed in red.

Serotonin Pharmacophore

- Sumatriptan and Dihydroergotamine are serotonin agonists used to treat migraine headaches
- Common pharmacophore across all three molecules is the indole ring followed by a two carbon linker connected to an amide. (Figure 1)
- Figure 2 highlights polar and non-polar bonds between Serotonin and amino acids within receptors 5-HT$_{1B}$ and 5-HT$_{2B}$.
- The positively charged nitrogen of the amide forms a bond with the carboxylate of the aspartic acid (D129 in 5-HT$_{1B}$).
- The nitrogen of the indole ring forms a hydrogen bond with the threonine amino acid (T134 in 5-HT$_{1B}$).
- Non-polar interaction between the benzene ring of the indole and serine.

Sequence Differences between 5-HT$_{1B}$ and 5-HT$_{1D}$

- To create a specific 5-HT$_{1B}$ agonist, amino acid differences between 5-HT$_{1B}$ and 5-HT$_{1D}$ could be exploited
- Figure 5 is a BLAST search comparing the amino acid sequences of 5-HT$_{1B}$ (bottom) and 5-HT$_{1D}$ (top). The differences between the two are highlighted in red.
- The amino acid sequences surrounding the serotonin pharmacophore shown above (D129 and T134) appear to be unchanged between the two receptors, offering little room to engineer selectivity.

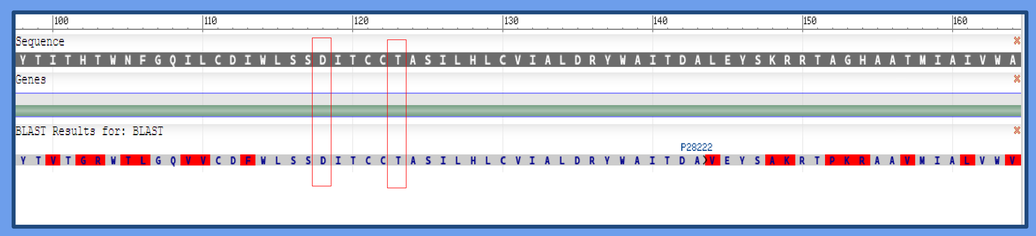
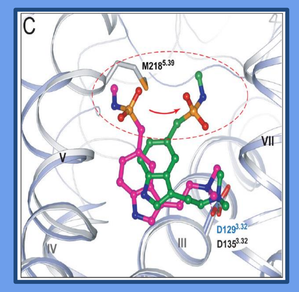


Fig. 5: A portion of the amino acid sequence of 5-HT$_{1D}$ is pictured on top, and 5-HT$_{1B}$ is on the bottom. The red highlighted sequences show amino acid sequence differences between the two proteins. Key serotonin pharmacophore binding amino acids D129 and T134 referenced above are boxed in red.

The Next Step

- Amino acid differences between the two receptors could potentially be exploited further up the sequence.
- Figure 6 shows how docking simulations along with the crystal structures were used to determine that a single amino acid difference, methionine (M218), is responsible for Sumatriptan having no activity in serotonin receptor 5-HT$_{2B}$.
- M218 allosterically blocks Sumatriptan from binding.
- Currently, receptor 5-HT$_{1D}$ has not been crystallized. If this were done, the same docking simulations could potentially identify possible binding site differences between 5-HT$_{1B}$ and 5-HT$_{1D.}$

Fig. 6: Sumatriptan bound to 5-HT$_{1B}$ (light blue) and 5-HT$_{2B}$ (black). Amino acid M218 in the 5-HT$_{2B}$ receptor blocks sumatriptan from binding to the active site, making it selective for 5-HT$_{1B.}$ M218 is an amino acid variant only found in receptor 5-HT$_{2B}$.[4]



Summary

Sumatriptan is an anti-migraine medication that is an agonist to 5-HT1B and 5-HT1D receptors. A common adverse side effect of this medication is a tightening sensation in the face, limbs, and/or chest nicknamed the “triptan sensation”. A randomized control trial showed that a 5-HT1D receptor agonist medication had no anti-migraine effect, yet several patients still experienced chest tightness. If a crystallized structure of 5-HT1D can be created, binding site differences between the two receptors could be explored to create a drug that is selective for just the 5-HT1B receptor. This could potentially lead to an anti-migraine drug without adverse side effects.

References

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